Report on the Deliberation Results

September 4, 2019

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Crysvita Subcutaneous Injection 10 mg Crysvita Subcutaneous Injection 20 mg Crysvita Subcutaneous Injection 30 mg
Non-proprietary Name	Burosumab (Genetical Recombination) (JAN*)
Applicant	Kyowa Kirin Co., Ltd.
Date of Application	January 7, 2019

Results of Deliberation

In its meeting held on August 29, 2019, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is classified as a biological product. The re-examination period is 10 years. The drug product and its drug substance are both classified as powerful drugs.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.

2. Since only a limited number of Japanese patients participated in the clinical studies of the product, the applicant is required to conduct a drug use-results survey involving all Japanese patients treated with the product after the market launch until data from a certain number of patients are gathered, to understand the characteristics of patients using the product and to promptly collect safety and efficacy data so that necessary measures are taken to ensure the proper use of the product.

**Japanese Accepted Name (modified INN)*

Review Report

August 8, 2019
Pharmaceuticals and Medical Devices Agency

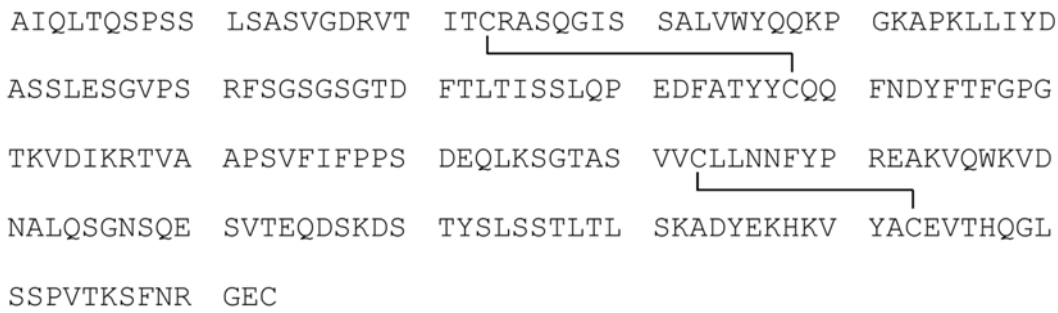
The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Crysvita Subcutaneous Injection 10 mg Crysvita Subcutaneous Injection 20 mg Crysvita Subcutaneous Injection 30 mg
Non-proprietary Name	Burosumab (Genetical Recombination)
Applicant	Kyowa Kirin Co., Ltd. (formerly Kyowa Hakko Kirin Co., Ltd.)
Date of Application	January 7, 2019
Dosage Form/Strength	Aqueous injection in vials, each (1 mL): containing 10 mg, 20 mg, or 30 mg of Burosumab (Genetical Recombination).
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Definition	Burosumab is a recombinant human IgG1 monoclonal antibody against fibroblast growth factor 23 (FGF23). Burosumab is produced in Chinese hamster ovary cells. Burosumab is a glycoprotein (molecular weight: ca. 147,000) composed of 2 H-chains (γ1-chains) consisting of 447 amino acid residues each and 2 L-chains (κ-chains) consisting of 213 amino acid residues each.

Structure

Amino acid sequence:

L-chain:



H-chain

QVQLVQSGAE VKKPGASVKV SCKASGYTFT NHYMHWVRQA PGQGLEWMGI

INPISGSTSN AQKFQGRVTM TRDTSTSTVY MELSSLRSED TAVYYCARDI

VDAFDFWGQG TMVTVSSAST KGPSVFPLAP SSKSTSGGTA ALGCLVKDYF

PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTQTYIC

NVNHKPSNTK VDKKVEPKSC DKTHTCPPCP APELLGGPSV FLFPPKPKDT

LMISRTPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQYNSTY

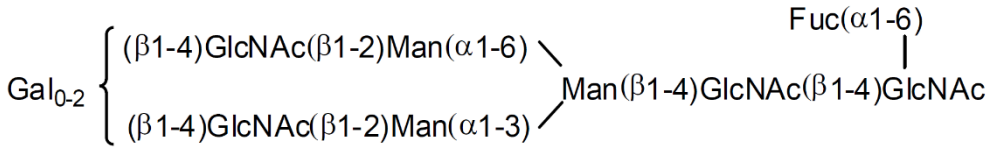
RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK GQPREPQVYT

LPPSRDELTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS

DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGK

Intrachain disulfide bonds: Solid lines
Interchain disulfide bonds: C213 in L-chain-C220 in H-chain, C226 in H-chain-C226 in H-chain, C229 in H-chain-C229 in H-chain
Pyroglutamate formation (partial): Q1 in H-chain
Glycosylation site: N297 in H-chain
Partial processing: K447 in H-chain

Putative structure of main carbohydrate chain:



Gal, galactose; GlcNAC, N-acetylglucosamine; Man, mannose; Fuc, fucose

Molecular formula: $C_{6388}H_{9904}N_{1700}O_{2006}S_{46}$ (protein portion)
Molecular weight: Approx. 147,000

Items Warranting Special Mention

Orphan drug (Orphan Drug Designation No. 415 of 2018 [*30 yaku*], PSEHB/PED Notification No. 0524-1 dated May 24, 2018, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

Reviewing Office Office of New Drug I

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of patients with FGF23-related hypophosphatemic rickets/osteomalacia, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions.

Indication

FGF23-related hypophosphatemic rickets/osteomalacia

Dosage and Administration

FGF23-related hypophosphatemic rickets/osteomalacia (except for tumor-induced osteomalacia)

The usual adult dosage is 1 mg/kg of burosumab (genetical recombination) injected subcutaneously once every 4 weeks. Each dose should not exceed 90 mg. The dose may be adjusted according to serum phosphorus concentration, clinical symptoms, etc.

The usual pediatric dosage is 0.8 mg/kg of burosumab (genetical recombination) injected subcutaneously once every 2 weeks. The dose may be adjusted according to serum phosphorus concentration, clinical symptoms, etc., up to the maximum of 2 mg/kg. However, the dose should not exceed 90 mg.

Tumor-induced osteomalacia

The usual adult dosage is 0.3 mg/kg of burosumab (genetical recombination) injected subcutaneously once every 4 weeks. The dose may be adjusted according to serum phosphorus concentration, clinical symptoms, etc., up to the maximum of 2 mg/kg.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.

2. Since only a limited number of Japanese patients participated in the clinical studies of the product, the applicant is required to conduct a drug use-results survey involving all Japanese patients treated with the product after the market launch until data from a certain number of patients are gathered, to understand the characteristics of patients using the product and to promptly collect safety and efficacy data so that necessary measures are taken to ensure the proper use of the product.

Attachment

Review Report (1)

June 27, 2019

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Crysvita Subcutaneous Injection 10 mg Crysvita Subcutaneous Injection 20 mg Crysvita Subcutaneous Injection 30 mg
Non-proprietary Name	Burosumab (Genetical Recombination)
Applicant	Kyowa Hakko Kirin Co., Ltd.
Date of Application	January 7, 2019
Dosage Form/Strength	Aqueous injection in vials, each (1 mL) containing 10 mg, 20 mg, or 30 mg of Burosumab (Genetical Recombination).

Proposed Indications

FGF23-related hypophosphatemic rickets/osteomalacia

Proposed Dosage and Administration

The usual adult dosage is 1 mg/kg of burosumab (genetical recombination) injected subcutaneously once every 4 weeks. The dose may be adjusted according to serum phosphorus concentration, clinical symptoms, etc. The maximum dose is 1 mg/kg or 90 mg, whichever is lower.

The usual pediatric dosage is 0.8 mg/kg of burosumab (genetical recombination) injected subcutaneously once every 2 weeks. The dose may be adjusted according to serum phosphorus concentration, clinical symptoms, etc., up to the maximum dose of 2 mg/kg or 90 mg, whichever is lower. Pediatric patients with bone age of ≥17 years (boys) or ≥15 years (girls) may follow the adult dosage regimen according to the patient's condition.

In patients with tumor-induced osteomalacia, the usual adult dosage is 0.5 mg/kg of burosumab (genetical recombination) injected subcutaneously once every 4 weeks. The dose may be adjusted according to serum phosphorus concentration, clinical symptoms, etc., up to the maximum of 2 mg/kg.

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List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Burosumab (Genetical Recombination) (hereinafter referred to as burosumab), discovered by Kyowa Hakko Kirin Co., Ltd., is a human immunoglobulin G (IgG)1 monoclonal antibody targeted at fibroblast growth factor 23 (FGF23). Burosumab binds to FGF23, thereby inhibiting the interaction between FGF23 and the complex of Klotho (a single-pass transmembrane protein) and fibroblast growth factor receptor (FGFR), and consequently inhibit FGFR-mediated intracellular signal transduction.

Calcium and phosphate are the major components of hydroxyapatite and are essential for the growth and mineralization of bones. Deficiency of either component causes bone and cartilage mineralization to be impaired, which leads to increased osteoid and results in reduced bone strength. Increased osteoid induces rickets in patients before the closure of growth plate cartilage, or osteomalacia in those with closed growth plates. Rickets and osteomalacia caused by decreased serum phosphorus concentration due to excess FGF23 production are defined as FGF23-related hypophosphatemic rickets/osteomalacia (*The Japanese journal of endocrinology*. 2015;91(suppl):1-11). Excess FGF23 production can be congenitally induced by the mutation of phosphate-regulating gene with homologies to endopeptidases on the X chromosome (*PHEX*) in germ cells or somatic cells, and this causes X-chromosome-linked hypophosphatemic rickets/osteomalacia (XLH), etc., while FGF23 can be produced excessively after birth mainly due to mesenchymal tumor, which causes tumor-induced osteomalacia (TIO).

FGF23 binds to Klotho/FGFR to form an FGF23-Klotho/FGFR complex. The complex acts to decrease serum phosphorus concentration through (a) the suppression of phosphate resorption due to decreased expression of type 2a and 2c sodium/phosphate cotransporter in proximal renal tubules and (b) the suppression of phosphate absorption from the intestinal tract due to decreased 1,25-dihydroxy vitamin D ($1,25(OH)_2D$) concentration in response to decreased expression of 25-hydroxyvitamin D (25(OH)D) -1α-hydroxylase responsible for $1,25(OH)_2D$ production. Burosumab is expected to improve hypophosphataemia in patients with FGF23-related hypophosphatemic rickets/osteomalacia through the neutralization of excess FGF23 observed in these patients.

Recently, the applicant submitted the marketing application for burosumab, having confirmed its efficacy and safety in patients with FGF23-related hypophosphatemic rickets/osteomalacia.

In foreign countries, burosumab was approved in the US in April 2018 for the indication of XLH in patients aged ≥1 year, and in Europe in February 2018 for the indication of XLH in children aged ≥1 year and adolescents. As of May 2019, burosumab is approved for the treatment of XLH in 35 countries including the US and European nations.

Burosumab is designated as an orphan drug with the intended indication for the treatment of FGF23-related hypophosphatemic rickets/osteomalacia (Orphan Drug Designation No. 415 of 2018 [*30 yaku*]), PSEHB/PED Notification No. 0524-1 dated May 24, 2018).

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Generation and control of cell substrate

Transgenic mice producing human IgG were immunized with human FGF23, and splenic cells obtained from the mice were fused with murine myeloma cells to prepare hybridoma cell lines. A gene expression construct encoding burosumab was prepared using (1) the gene fragments encoding the variable regions of the light and heavy chains of the anti-human FGF23 antibody obtained from the hybridoma cell lines and (2) the expression plasmid containing the constant region of human IgG1. The gene expression construct thus obtained was introduced into CHO cell line, and master cell bank (MCB) and working cell bank (WCB) were prepared from the clone best suited for the manufacture of burosumab.

Characterization and purity test of MCB, WCB, and "cells at the limit of in vitro cell age used for production" (CAL) were conducted in accordance with the International council for harmonization of technical requirements for pharmaceuticals for human use (ICH) Guidelines "Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin" (PMSB/ELD Notification No. 329, dated February 22, 2000) [ICH Q5A (R1)], "Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of R-DNA Derived Protein Products" (PMSB/ELD Notification No. 3, dated January 6, 1998 [ICH Q5B], and "Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products" (PMSB/ELD Notification No. 873, dated July 14, 2000 [ICH Q5D]). The results of the tests conducted confirmed the genetic stability of MCB, WCB, and CAL during the manufacturing period, and did not detect viral or non-viral adventitious agents except for endogenous retrovirus-like particles commonly observed in cell lines of rodent origin.

MCB and WCB are stored in the gaseous phase of liquid nitrogen. There is no plan for regeneration of MCB, while WCB will be regenerated as necessary.

2.1.2 Manufacturing process

The manufacturing process of the drug substance comprises preculture, main culture, harvesting, [redacted] chromatography, virus inactivation at low pH, [redacted] chromatography, [redacted] chromatography, virus removal by filtration, concentration/buffer replacement, preparation/filling of drug solution, and test/storage.

The following steps are defined as critical steps: [redacted], [redacted] chromatography, [redacted], [redacted] chromatography, [redacted] chromatography, [redacted], and [redacted] processes.

The manufacturing process of the drug substance was validated on a commercial scale.

2.1.3 Safety evaluation of adventitious infectious agents

No raw materials of biological origin, except for the CHO cell line, host cell, are used in the manufacturing process of the drug substance.

Purity tests were performed on the MCB, WCB, and CAL [see Section "2.1.1 Generation and control of cell substrate"]. An unprocessed bulk manufactured on a commercial scale was subjected before harvest to mycoplasma testing, bioburden testing, adventitious virus testing, and transmission electron microscopy. The results showed that the bulk was not contaminated by viral or non-viral adventitious agents. Mycoplasma testing, adventitious virus testing, and mouse minute virus testing for unprocessed bulk before harvest are performed as in-process control tests.

A viral clearance study was performed with model viruses for the purification processes. The results showed that the purification processes have a sufficient viral clearance capacity (Table 1).

Table 1. Results of viral clearance study

Manufacturing process	Viral reduction factor (log_{10})			
	Xenotropic murine leukemia virus	Minute virus of mice	Pseudorabies virus	Reovirus type 3
[redacted] chromatography	[redacted]	[redacted]	[redacted]	[redacted]
Virus inactivation at low pH	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] chromatography	[redacted]	[redacted]	[redacted]	[redacted]
Virus removal by filtration	[redacted]	[redacted]	[redacted]	[redacted]
Overall reduction factor	≥18.66	≥11.11	≥17.91	≥12.35

2.1.4 Manufacturing process development

The following were main changes made in the manufacturing method during the development of the drug substance (Method A, Method B, Method C, or the proposed method). Phase I studies used the formulation prepared from the drug substance manufactured by Method A, Method B, or Method C, phase I/II studies used the formulation prepared from the drug substance manufactured by Method B or Method C, and phase II and III studies used the formulation prepared from the drug substance manufactured by Method C or the proposed method [see Section "6.1 Summary of biopharmaceutic studies and associated analytical methods"].

- From Method A to Method B: Change in neutralization conditions after virus inactivation at low pH, change in [redacted], etc.
- From Method B to Method C: Change in [redacted], [redacted], [redacted], [redacted], etc.
- From C to the proposed method: Changes in [redacted], [redacted], [redacted], [redacted], etc.

Comparability of the drug substance before and after each change was confirmed by tests on quality attributes.

A quality-by-design (QbD) approach was used in the development of the manufacturing process [see Section "2.3 QbD"].

2.1.5 Characterization

2.1.5.1 Structure and properties

Characterization studies were conducted as shown in Table 2.

Table 2. Parameters evaluated by characterization studies

Primary structure/higher order structure	Amino acid sequence, N-terminal and C-terminal amino acid sequences, posttranslational modification, disulfide linkages, secondary structure, tertiary structure, thermal stability
Physicochemical properties	Molecular weight, extinction coefficient, charge variants, size variants
Carbohydrate structure	Binding sites of N-linked oligosaccharides, glycosylation rate, structural analysis of N-linked oligosaccharides, oligosaccharide profile, analysis of monosaccharide components
Biological properties	[redacted] activity
	FcγRI, FcγRIIa, FcγRIIb, FcγRIIIa (V), FcRn, [redacted] activities
	[redacted] activity
	[redacted] activity, [redacted] activity

Studies on biological properties were conducted, including:

- The binding activity of burosumab to [redacted] and [redacted] was evaluated by [redacted] and [redacted], respectively.

- The binding activity of burosumab to Fc gamma receptor (FcγR)I, FcγRIIa, FcγRIIb, FcγRIIIa (V), and neonatal Fc receptor (FcRn) in Fc region was evaluated by [redacted].

- Using recombinant [redacted] cell line introduced with [redacted] and [redacted] ([redacted] cells), the neutralizing activity of burosumab was evaluated based on the inhibition of binding of FGF23 to the receptor as an indicator.

- Using [redacted] cell line as the target cells and [redacted] cell line prepared by engineering [redacted] cells to express FcγRIIIa (V) as the effector cells, antibody dependent cellular cytotoxicity (ADCC) activity of burosumab in the presence of FGF23 was confirmed. Complement dependent cytotoxicity (CDC) activity was evaluated using [redacted] compliment and [redacted] cell line in the presence of FGF23. No CDC activity was observed.

2.1.5.2 Product-related substances/Product-related impurities

Based on the results of the characterization described in Section "2.1.5.1 Structure and properties," the following were identified as product-related substances: [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted]. Also, Impurities A and B were identified as product-related impurities. The product-related impurities are appropriately controlled by the specifications and testing for both drug substance and the drug product.

2.1.5.3 Process-related impurities

Host cell protein (HCP), host-derived DNA, [redacted], [redacted], [redacted], [redacted], and [redacted] were identified as process-related impurities. It was confirmed that all process-related impurities were sufficiently removed in the manufacturing process.

2.1.6 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (enzyme-linked immunosorbent assay [ELISA] and peptide mapping), pH, [redacted], purity ([redacted]-high performance liquid chromatography [HPLC], [redacted], [redacted], and [redacted]-HPLC), bacterial endotoxin, microbial limit, bioactivity (FGF23-neutralizing activity), and assay

(ultraviolet-visible spectrophotometry). [redacted] was added to the specifications during the review process after application [see Section "2.R.1 Control of ADCC activity"].

2.1.7 Stability of drug substance

Table 3 shows the main stability studies of the drug substance.

Table 3. Outline of main stability studies of drug substance

	Manufacturing method	Number of batches	Storage conditions	Study period	Storage package
Long-term testing	Method C	4	−40 ± 10°C	[redacted] months	[redacted] container
	Proposed method	5		[redacted] months[a)]	
Accelerated testing	Proposed method	5	5 ± 3°C	[redacted] months	
Stress testing	Proposed method	1	25 ± 2°C, 40 ± 5% RH	[redacted] months	
	Proposed method	1	40 ± 2°C, 35 ± 5% RH	[redacted] months	
Photostability testing	Proposed method	1	5 ± 3°C	Overall illumination of ≥1.2 million lx·h, an integrated near ultraviolet energy of ≥200 W·h/m^2	

a) [redacted]-month stability study completed in 1 batch and [redacted]-month stability tests completed 2 batches, and [redacted]-month stability test ongoing in 2 batches.

The long-term storage testing did not show any change in the quality attributes throughout the study period.

The accelerated testing showed slight changes in [redacted] and [redacted] in [redacted].

The stress testing ([redacted] ± [redacted]°C, [redacted] ± [redacted]% RH) showed decreased [redacted] at [redacted]; a tendency of an increase in Impurities B1 and B2, decreased [redacted], and increased [redacted] at [redacted]; decreased [redacted] and increased Impurity B1 at [redacted]; and increased [redacted], decreased [redacted], a tendency of a decrease in [redacted] and [redacted], etc., at [redacted].

The stress testing ([redacted] ± [redacted]°C, [redacted] ± [redacted]% RH) showed a tendency of an increase in Impurity A1 at [redacted], increased Impurities B1 and B2 at [redacted], decreased [redacted], etc., in addition to the changes observed in the stress testing ([redacted] ± [redacted]°C, [redacted] ± [redacted]% RH).

Photostability testing showed that the drug substance was photounstable.

Based on the above, the shelf life of [redacted] months has been proposed for the drug substance when stored in [redacted] container at [redacted] ± [redacted]°C, protected from light.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is an aqueous injection containing 10 mg, 20 mg, or 30 mg of burosumab per glass vial (5 mL). The drug product contains L-histidine, [redacted], polysorbate 80, L-methionine, [redacted], and water for injection as excipients.

2.2.2 Manufacturing process

The manufacturing process of the drug products is comprised of the following steps: Thawing of the drug substance, preparation of drug solution, sterile filtration, filling/capping/clamping, labeling/packaging, and testing/storage.

[redacted], [redacted], and [redacted] are defined as critical steps.

The manufacturing process of the drug product was validated on a commercial scale.

2.2.3 Manufacturing process development

The following are main changes made in the drug product manufacturing process during the development (Methods 1, 2, 3, and proposed method). The phase I studies used the formulation manufactured by Methods 1, 2, and 3; the phase I/II study used the formulation manufactured by Methods 2 and 3; and the phase II and phase III studies used the formulation manufactured by Method 3 and the proposed method [see Section "6.1 Summary of biopharmaceutic studies and associated analytical methods"].

- From Method 1 to Method 2: Change in [redacted], etc.
- From Method 2 to Method 3: Change in [redacted], etc.
- From Method 3 to proposed method: Changes in [redacted], [redacted], etc.

Comparability of the drug product before and after each change was confirmed by tests on quality attributes.

A QbD approach was used in the development of the manufacturing process [see Section "2.3 QbD"].

2.2.4 Control of drug product

The proposed specifications for the drug product consist of content, description, identification (ELISA), osmotic ratio, pH, purity ([redacted]-HPLC, [redacted], [redacted], and [redacted]-HPLC), polysorbate 80, methionine, extractable volume, foreign insoluble matters, insoluble particulate matters, sterility, bioactivity (FGF23-neutralizing activity), and assay (ultraviolet-visible spectrophotometry).

2.2.5 Stability of drug product

Table 4 shows main stability studies of the drug product. The studies employed a bracketing method so that testing on 20-mg formulation was omitted.

Table 4. Outline of the main stability study of the drug product

	Formulation	Number of batches[a)]	Storage conditions	Study period	Storage package
Long-term testing	10 mg	4	5 ± 3°C	36 months	Glass vial with butyl rubber cap
	20 mg	1		24 months[b)]	
	30 mg	4		36 months	
Accelerated testing	10 mg	4	25 ± 2°C 60 ± 5% RH	6 months	
	20 mg	1			
	30 mg	4			
Stress testing	10 mg	1	40 ± 2°C 75 ± 5% RH	1 month	
	20 mg	1			
	30 mg	1			
Photostability testing	10 mg	1	5 ± 3°C	Total illumination of ≥1.2 million lx·h, an integrated near ultraviolet energy of ≥200 W·h/m^2	
	30 mg	1			

a) Drug product manufactured by the proposed method from the drug substance prepared by the proposed method.
b) The stability study is ongoing up to 36 months.

The long-term testing showed a tendency of an increase in [redacted] and a tendency of a decrease in [redacted] at [redacted]. No significant changes were observed in other quality attributes throughout the study period.

The accelerated testing and the stress testing showed decreased [redacted] at [redacted]; decreased [redacted] and increased [redacted] at [redacted]; decreased [redacted] and increased Impurity B1 at [redacted]; increased [redacted], decreased [redacted], a tendency of a decrease in [redacted], and decreased [redacted], etc., at [redacted]

Photostability testing showed that the drug product was photounstable.

Based on the above, the shelf life of 36 months was proposed for the drug product when stored in a primary container consisting of a glass vial with a butylrubber stopper and in a paper box (secondary container) at 5 ± 3°C, protected from light.

2.3 QbD

The strategy for quality control was developed by the following investigations, etc., using a QbD approach.

- Identification of critical quality attributes (CQAs)
  The following CQAs were identified from among the quality attributes including product-related substances, product-related impurities, process-related impurities [see Sections "2.1.5.2 Product-related substances/Product-related impurities" and "2.1.5.3 Process-related impurities"], and formulation attributes, based on the information obtained during the development of burosumab and related findings.

CQAs of the drug substance: [redacted], [redacted], HCP, host cell-derived DNA, [redacted], bacterial endotoxin, microorganisms, mycoplasmas, viruses, [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted],

[redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted]

CQA of the drug product: [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], impurities derived from the drug substance manufacturing process (HCP, host cell-derived DNA, [redacted], bacterial endotoxin, microorganisms, mycoplasmas, viruses [redacted], [redacted], [redacted]), [redacted], [redacted] and [redacted], [redacted], [redacted], microorganisms. [redacted], [redacted], [redacted], bioactivity, and protein content.

- Characterization of process
  Processes that affect the CQAs were identified. Then, in these processes, process control parameters significantly affecting the CQAs and process performance were identified by means of risk assessment, etc. The acceptable range and the robustness of these process control parameters were confirmed.

- Establishment of control method
  Based on knowledge on the processes including the characterization of the above processes, batch analysis results, stability studies results, etc., the method for controlling the quality attributes of burosumab was established by the combination of the control of process parameters and performance attributes, in-process control, and specifications [for the control of product-related impurities and process-related impurities, see Sections "2.1.5.2 Product-related substances/Product-related impurities" and "2.1.5.3 Process-related impurities"].

2.R Outline of the review conducted by PMDA

On the basis of the submitted data and the results of the following review, PMDA has concluded that the quality of the drug substance and the drug product is controlled in an appropriate manner.

2.R.1 Control of ADCC activity

ADCC activity was detected in the characterization studies of burosumab [see Section "2.1.5.1 Structure and properties"]. The applicant considered that the control of ADCC activity in the drug substance or the drug product is unnecessary for the following reasons: (1) no clear changes were observed in ADCC activity and associated oligosaccharide profiles in the long-term testing; and (2) ADCC activity of burosumab is unlikely to affect the safety, judging from the results of clinical studies, etc.

A degree of influence of burosumab's ADCC activity on its clinical efficacy and safety observed in the characterization study is unknown. PMDA, recognizing the importance of appropriate control on the ADCC activity and the oligosaccharide profile (content of afucosylated carbohydrates) related to the ADCC activity, requested the applicant to consider possible actions.

The applicant responded that the oligosaccharide profile (content of afucosylated carbohydrates) related to the ADCC activity will be included in the specification for control.

PMDA confirmed that the applicant took an appropriate measure and accepted it.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

The following primary pharmacodynamic studies of burosumab were conducted: (1) *in vitro* studies on the mechanism of action of burosumab, binding affinity to FGF23 among others; and (2) *in vivo* studies on the effect on serum phosphorus concentration, $1,25(OH)_2D$ concentration, etc., in normal animals and in model animals of XLH. Also, safety pharmacology studies were conducted to investigate the effect on the central nervous system, cardiovascular system, and respiratory system. Secondary pharmacology studies and pharmacodynamic interaction studies were not conducted. Results of the main studies are described below.

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 Binding affinity of burosumab to FGF23 (CTD 4.2.1.1-1)

The binding affinity of burosumab for FGF23 of humans, cynomolgus monkeys, and rabbits was investigated. The dissociation constant of burosumab in complex with FGF23 of humans, cynomolgus monkeys, and rabbits[1)] was 30, 39, and 63 pmol/L, respectively.

3.1.1.2 Inhibition of FGF23-mediated signal transduction (CTD 4.2.1.1-4 and 4.2.1.1-8)

The inhibition of FGF23-mediated signal transduction by the burosumab-human FGF23 complex was investigated by a reporter assay using human embryonic kidney (HEK) cells that were engineered to co-express human Klotho and FGFR and introduced with luciferase gene into the promoter region of early growth response transcription factor 1 (Egr-1). Human FGF23 (0.1-100 ng/mL)-mediated signal transduction was inhibited by burosumab in a concentration-dependent manner at ≤100 ng/mL, with the inhibition rate for without addition of burosumab being ≥85% at ≥1000 ng/mL.

The signal transduction mediated by mouse FGF23 (10 and 100 ng/mL), the receptor which burosumab does not bind to nor inhibit, decreased in the presence of the complex of burosumab and human FGF23 (1000-10000 ng/mL) in a manner dependent on the concentration of the complex.

3.1.2 *In vivo* studies

3.1.2.1 Single intravenous administration study in cynomolgus monkeys (CTD 4.2.1.1-10 and 4.2.1.1-11)

A single dose of burosumab (1, 3, or 10 mg/kg) or vehicle[2)] was administered intravenously to cynomolgus monkeys (2-3 years old, 3/sex/group), and serum phosphorus, calcium, parathyroid hormone (PTH), and $1,25(OH)_2D$ concentrations and urinary phosphate concentration, etc., were measured up to 72 hours after the administration of vehicle and up to 168 hours after the administration of burosumab.

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1) Data are the mean of triplicate experiments (human and cynomolgus monkey FGF23) and the result of a single experiment (rabbit FGF23).
2) 10 mmol/L sodium glutamate, 262 mmol/L D-sorbitol, 0.05 mg/mL polysorbate 80

Urinary phosphate concentration did not significantly differ between vehicle and burosumab. In contrast, serum phosphorus concentration, the ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR), and serum $1,25(OH)_2D$ concentration increased up to 72 hours after administration in all burosumab groups. Also, serum calcium slightly increased in the 3 and 10 mg/kg groups and serum PTH slightly decreased in the 3 and 10 mg/kg groups as compared with the vehicle group at some of the measuring time points.

3.1.2.2 Single intravenous administration in cynomolgus monkeys (CTD 4.2.1.1-14)

A single dose of burosumab (0.001, 0.003, 0.01, 0.03, or 0.1 mg/kg) or vehicle[3)] was administered intravenously to cynomolgus monkeys (6-7 months old, 3 males/group), and serum concentrations of phosphate, calcium, PTH, $1,25(OH)_2D$, etc., were measured up to Day 28 after administration.

Serum phosphorus concentration tended to an increase from 24 hours after administration up to Day 14 in the ≥0.03 mg/kg groups than in the vehicle group. Serum $1,25(OH)_2D$ concentration increased at 8 hours after administration in the ≥0.003 mg/kg groups, up to Day 1 in the 0.003 to 0.03 mg/kg groups, and up to Day 3 in the 0.1 mg/kg group, compared with the vehicle group. Neither serum calcium nor PTH concentration changed in any of the burosumab groups as compared with the vehicle group.

3.1.2.3 Thirteen-week repeated subcutaneous administration study in cynomolgus monkeys (CTD 4.2.1.1-15)

Burosumab (1 mg/kg) was administered subcutaneously to cynomolgus monkeys (7-8 months old, 4/sex/group; 4-6 years old, 4/sex/group) once every 2 weeks for 13 weeks, and serum phosphorus concentration, etc., were measured up to Day 56 after the last dose.

Serum phosphorus concentration increased from 8 hours after the first dose in 7- to 8-month old females, and from 72 hours after the first dose in other groups. Serum phosphorus concentration after the last dose showed a change over time similar to that observed after the first dose in all groups, and returned to the baseline level before Day 28 after the last dose.

3.1.2.4 Effect in animal model of XLH (CTD 4.2.1.1-16 [Reference data])

Murine anti-FGF23 antibody[4)] (4 or 16 mg/kg) or the control antibody[5)] was administered subcutaneously once every week for 5 weeks to male hypophosphatemic (Hyp) mice (4-week old), a pathological animal model of XLH, and wild type (WT)[6)] mice. Table 5 shows the results with each parameter after administration. In the group receiving murine anti-FGF23 antibody, serum phosphorus concentration increased to an equal or greater extent than in the WT group, and fractional excretion of phosphate decreased with an increase in anti-FGF23 antibody dose as compared with the control group of Hyp mice.

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3) 10 mmol/L L-histidine, 252 mmol/L D-sorbitol, 0.5 mg/mL polysorbate 80, 10 mmol/L L-methionine

4) FN1 (IgG1 that recognizes the N-terminus of mouse FGF23) and FC1 (IgG1 that recognizes the C-terminus of mouse FGF23) were mixed in at a ratio of 1 to 1. Murine anti-FGF23 antibodies were used because burosumab does not cross-react with mouse FGF23.

5) Mouse monoclonal antibody against human thrombopoietin (16 mg/kg)

6) Normal male mice that are litter mates of male Hyp mice born to female mice with hetero deficiency of *PHEX* gene as a result of copulation with male C57BL/6J mice

Table 5. Concentration of each analyte after antibody administration

Analyte	Measuring time point	WT mice	Hyp mice		
		Control antibody 16 mg/kg (n = 7)	Control antibody 16 mg/kg (n = 7)	Anti-FGF23 antibody 4 mg/kg (n = 5)	Anti-FGF23 antibody 16 mg/kg (n = 7)
Serum phosphorus (mg/dL)	Day 31	7.6 ± 0.3	5.1 ± 0.2	7.6 ± 0.4	11.6 ± 0.9
Serum calcium (mg/dL)	Day 31	8.6 ± 0.3	8.0 ± 0.3	8.2 ± 0.2	9.2 ± 0.1
Serum 1,25$(OH)_2$D (pg/mL)	Day 29	139 ± 14	137 ± 8	1007 ± 19	901 ± 25
Serum PTH (pg/mL)	Day 31	38.8 ± 5.2	72.3 ± 12.0	NC[b)]	30.0 ± 1.4
Fractional excretion of phosphate[a)] (%)	Day 31	17.7 ± 1.1	38.4 ± 4.8	33.3 ± 3.8	21.4 ± 2.1

Mean ± standard error (SE); NC, Not calculated
a) Phosphate clearance divided by creatinine clearance
b) Serum could not be obtained in a required amount.

In both groups receiving murine anti-FGF23 antibody, body features characteristic to Hyp mice, i.e., short tail and hypertrophic and deformed epiphyses and diaphysis, were less obvious than in the Hyp mouse group receiving control antibody, and elongation of thigh and shin bones was observed. Also, body weight gain was observed.

In the histological examination, both groups receiving murine anti-FGF23 antibody showed improvement in disordered columnar structure of chondrocytes in the proximal epiphyseal growth plates, increased hypertrophic chondrocytes, abnormal thickening of the growth plate structures, which were observed in the Hyp mouse group receiving control antibody. Decreased osteoids and increased calcified bones in sponge bones or cortical bones of shin bones were observed. In the group receiving murine anti-FGF23 antibody (16 mg/kg), the rates of calcification and bone formation were approximately 70% of those in the WT group.

3.1.2.5 Effect in animal model of XLH (CTD 4.2.1.1-17 [Reference data])

Murine anti-FGF23 antibody[4)] (4 or 16 mg/kg) or the control antibody[5)] was administered subcutaneously once every week for 8 weeks to male Hyp mice (21-week old). Table 6 shows the results of measurement of each parameter after administration. In both groups receiving FGF23 antibody, concentrations of serum phosphorus, calcium, and 1,25$(OH)_2$D increased as compared with the control antibody group, and reduced body weight gain also improved.

Table 6. Concentration of each analyte after antibody administration

Analyte	Measuring time point	WT mice	Hyp mice		
		Control antibody 16 mg/kg (n = 9)	Control antibody 16 mg/kg (n = 10)	Anti- FGF23 antibody 4 mg/kg (n = 10)	Anti- FGF23 antibody 16 mg/kg (n = 10)
Serum phosphorus (mg/dL)	Day 50	5.4 ± 0.3	2.3 ± 0.1	5.6 ± 0.2	7.3 ± 0.2
Serum calcium (mg/dL)	Day 50	9.4 ± 0.1	8.9 ± 0.1	9.6 ± 0.1	9.9 ± 0.2
Serum 1,25$(OH)_2$D (pg/mL)	Day 50	172 ± 6	177 ± 10	660 ± 27	474 ± 29
Serum PTH (pg/mL)	Day 56	20.4 ± 3.5	37.8 ± 8.8	50.8 ± 7.3	25.8 ± 7.7
Body weight (g)	Day 50	35.5 ± 1.3	24.4 ± 0.7	26.8 ± 0.4	27.9 ± 0.7
Change in body weight (g)[a)]	-	1.0 ± 0.5	0.3 ± 0.3	3.2 ± 0.4	4.1 ± 0.2

Mean ± SE; -, Not applicable
a) Change from baseline to Day 56

Both groups receiving murine anti-FGF23 antibody showed increased bone ash of the tibias, increased osteoid in the femurs, and increased gripping power of fore- and hind-limbs as compared with the control

antibody group, whereas no improvement was observed in the deformed femurs, length of long bones, and weight of quadriceps muscles.

3.2 Safety pharmacology

Table 7 shows the effect of burosumab on the central nervous, cardiovascular, and respiratory systems, all of which were investigated in repeated-dose toxicity studies [see Section "5.2 Repeated-dose toxicity"].

Table 7. Outline of the results of safety pharmacology studies

Organ system	Test system	Endpoints and methods	Dosage regimen of burosumab	Route of administration	Findings	CTD
Cardiovascular/ respiratory system	Cynomolgus monkeys (4/sex/group)	Blood pressure, ECG, respiratory rate	0, 0.03, 0.3, 3, 30 mg/kg Once every 2 weeks for 14 weeks	IV	No effect on cardiovascular and respiratory system	4.2.3.2-3
Central nervous/ cardiovascular system	Cynomolgus monkeys (4/sex/group)	Clinical signs, blood pressure, ECG, cardiac function	0, 0.03, 0.3, 3, 30 mg/kg Once every 2 weeks for 40 weeks	IV	A significant increase[a] in heart rate was observed at Week 39 in males in the 30 mg/kg group compared with the control group, but resolved during the recovery period. No effect on the central nervous system	4.2.3.2-4
			30 mg/kg Once every 2 weeks for 40 weeks	SC.	No effect on cardiovascular and central nervous system	
	Juvenile cynomolgus monkeys (4/sex/group)	Clinical signs, blood pressure, ECG	0, 0.03, 0.3, 3 mg/kg Once every 2 weeks for 40 weeks	IV.	No effect on cardiovascular and central nervous system	4.2.3.2-5
			3 mg/kg Once every 2 weeks for 40 weeks	SC		

a) Observed at supraphysiological concentrations of serum phosphorus concentration (>8 mg/dL), suggesting that the result was related to the mineral deposition to cardiac muscle fibers/myocardial vessels or to the media layer of the aorta, and that the change was caused by the excessive pharmacological response to burosumab in normal animals.

3.R Outline of the review conducted by PMDA

3.R.1 Pharmacological action of burosumab

The applicant's explanation:

FGF23 binds to Klotho/FGFR to form the complex that decreases serum phosphorus concentration through (1) the inhibition of phosphate resorption by decreased expression level of the type 2a and 2c sodium/phosphate co-transporters in the proximal renal tubules and (2) the inhibition of phosphate absorption from the intestinal tract through decreased $1,25(OH)_2D$ concentration caused by decreased expression level of 25-hydroxyvitamin D-1α-hydroxylase responsible for $1,25(OH)_2D$ production (*J Endocrinol.* 2007;194:1-10, *J Bone Miner Res.* 2008;23:1509-18, etc.). *In vitro* studies showed that burosumab, a human IgG1 monoclonal antibody that binds to FGF23, has affinity for human, monkey, and rabbit FGF23 (CTD 4.2.1.1-1) and inhibits the signal transduction mediated by forming the complex with FGF23 that neutralizes FGF23 (CTD 4.2.1.1-4). *In vivo* studies showed that burosumab increased phosphate and $1,25(OH)_2D$ concentrations in serum in rabbits and cynomolgus monkeys. An *in vivo* study in an animal model of XLH, the administration of anti-FGF23 antibody to juvenile Hyp mice led to increased serum phosphorus concentration, decreased fractional phosphate excretion rate, improved elongation of thigh bones and shin bones, improved columnar structure in both chondrocytes and cortical

bone of the proximal epiphyseal growth plates, decreased osteoids, and increased mineralized bones. In addition, mature Hyp mice showed increased serum phosphorus, calcium, and $1,25(OH)_2D$ concentrations and improved gripping power.

These results suggest that burosumab inhibits signal transduction mediated by excess level of FGF23 observed in patients with XLH, increases phosphate resorption in the kidney, thereby improving hypophosphatemia, leading to normalization or improvement in most of the abnormalities characteristic to XLH (rickets/osteomalacia, muscular weakness, and pain). Increased serum phosphorus concentration was confirmed in the study using Hyp mice, demonstrating the benefit of burosumab for XLH, which suggests that burosumab is useful as well for other FGF23-related hypophosphatemic rickets/osteomalacia caused by decreased serum phosphorus concentration due to FGF23 overexpression as is the case with XLH.

PMDA's view:
The submitted *in vitro* study data demonstrate the FGF23-neutralizing activity of burosumab, and the *in vivo* study data show that burosumab increases serum phosphorus concentration. In an animal model of XLH, anti-FGF23 antibody are shown to increase serum phosphorus concentration and improve abnormalities characteristic of XLH. These results suggest that burosumab has promising efficacy in the treatment of hypophosphatemic rickets/osteomalacia caused by excess FGF23.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

The pharmacokinetics of a single dose of subcutaneous or intravenous burosumab was investigated in rabbits and monkeys. Also, based on the toxicokinetics in toxicity studies in rabbits and monkeys, the pharmacokinetics of repeated doses of burosumab was investigated. Serum burosumab concentration was measured by chemiluminescence immunoassay. The lower limit of quantitation was 100 ng/mL in rabbits and 30 ng/mL in monkeys. The anti-burosumab antibody was measured by surface plasmon resonance or by ELISA. Main study results are described below.

4.1 Absorption

4.1.1 Single-dose administration (CTD 4.2.1.1-13 and 4.2.3.1-1)

Table 8 shows pharmacokinetic parameters observed following a single intravenous or subcutaneous dose of burosumab to male and female rabbits and male monkeys.

Table 8. Pharmacokinetic parameters following a single-dose of burosumab

Animal species	Route of administration	Dose (mg/kg)	Sex	N	C_{max} (μg/mL)	AUC_{inf} (μg•h/mL)	t_{max} (h)	$t_{1/2}$ (h)	CL[a)] (mL/h/kg)	V_{ss}[b)] (mL/kg)	F (%)
Rabbits	IV	0.03	M	8	0.770 ± 0.101	127 ± 67	NC	NC	NC	NC	NC
			F	8	0.857 ± 0.175	52 ± 28	NC	NC	NC	NC	NC
		0.3	M	8	10.5 ± 3.13	984 ± 114	NC	NC	NC	NC	NC
			F	8	9.14 ± 1.89	785 ± 165	NC	NC	NC	NC	NC
		3	M	10	88.5 ± 10.9	6792 ± 1804	NC	NC	NC	NC	NC
			F	10	81.4 ± 17.1	4645 ± 631	NC	NC	NC	NC	NC
Monkeys	IV	0.03	M	4	1.39 ± 0.06	233 ± 57	NC	186 ± 52	0.135 ± 0.033	37.0 ± 2.7	NC
		0.3		4	11.4 ± 0.7	1570 ± 370	NC	172 ± 47	0.199 ± 0.039	49.1 ± 5.5	NC
		3		4	83.3 ± 11.3	13700 ± 1800	NC	216 ± 17	0.222 ± 0.031	73.9 ± 8.5	NC
	SC	0.03		4	0.516 ± 0.033	201 ± 48	72 ± 0	219 ± 67	0.156 ± 0.038	46.8 ± 4.3	86.4 ± 20.7
		0.3		4	4.61 ± 0.81	2150 ± 630	60 ± 24	310 ± 61	0.148 ± 0.037	63.6 ± 6.5	136.8 ± 40.3
		3		4	30.9 ± 4.3	10800 ± 900	96 ± 28	259 ± 42	0.279 ± 0.024	104 ± 22	79.1 ± 6.9

Mean ± standard deviation (SD); NC, Not calculated

C_{max}, Maximum serum concentration; AUC_{inf}, Area under serum concentration-time curve from time 0 to infinity; t_{max}, Time to maximum serum concentration; $t_{1/2}$, Elimination half-life; CL, Apparent total clearance; V_{ss}, Apparent distribution volume; F, Bioavailability.

a) CL/F in subcutaneous administration

b) V_z/F in subcutaneous administration

4.1.2 Repeat-dose administration (CTD 4.2.3.2-1 to 4.2.3.2-4, and 4.2.3.5.3-1)

Table 9 shows the pharmacokinetic parameters of burosumab administered once every 2 weeks to male and female rabbits, male and female monkeys, and pregnant monkeys. The anti-burosumab antibody was not detected in any male or female rabbits receiving the 14-week repeated doses, and detected in 2 of 4 males among male and female monkeys receiving 3 mg/kg for 14 weeks and 1 of 8 males among male and female monkeys receiving 30 mg/kg intravenous doses for 40 weeks.

Table 9. Pharmacokinetic parameters following repeated doses of burosumab once every 2 weeks

Animal species	Route of administration	Dose (mg/kg)	N	Measuring time point	C_{max} (μg/mL)		AUC[a] (μg•h/mL)	
					Male	Female	Male	Female
Rabbits	IV	0.03	4	Week 1	1.17 ± 0.08	1.25 ± 0.17	123 ± 7	112 ± 29
				Week 13	1.24 ± 0.08	1.17 ± 0.20	112 ± 11	111 ± 27
		0.3	4	Week 1	10.8 ± 0.5	11.0 ± 0.5	1020 ± 98	928 ± 34
				Week 13	12.5 ± 1.3	11.3 ± 1.6	1310 ± 103	1230 ± 225
		3	4	Week 1	96.8 ± 3.8	99.4 ± 3.1	9030 ± 2310	7060 ± 1430
				Week 13	113 ± 2[b]	109 ± 16	14000 ± 2290[b]	9750 ± 2620
Monkeys	IV	0.03	4	Week 1	0.922 ± 0.071	1.11 ± 0.23	88 ± 10	102 ± 19
				Week 13	1.83 ± 0.21	1.29 ± 0.12	226 ± 38	142 ± 16
		0.3	4	Week 1	13.0 ± 1.6	12.2 ± 1.2	1496 ± 133	1381 ± 282
				Week 13	17.3 ± 1.1	19.3 ± 6.5	2319 ± 479	2601 ± 1172
		3	4	Week 1	142 ± 15	125 ± 14	14201 ± 3025	13318 ± 2430
				Week 13	187, 208[c]	176 ± 41	19929, 33397[c]	24955 ± 8929
		30	6	Week 1	1275 ± 184	1259 ± 103	141561 ± 14449	135889 ± 11782
				Week 13	1658 ± 220	1563 ± 225	215835 ± 37286	228007 ± 77567
Monkeys	IV	0.03	4	Week 1	NC	NC	159 ± 7	141 ± 25
			4	Week 13	NC	NC	267 ± 11	232 ± 63
			4	Week 39	NC	NC	376 ± 41	298 ± 100
		0.3	4	Week 1	NC	NC	1270 ± 160	1270 ± 90
			4	Week 13	NC	NC	1850 ± 160	2850 ± 450
			4	Week 39	NC	NC	2300 ± 390	2910 ± 330
		3	4	Week 1	NC	NC	20600 ± 4300	13800 ± 2000
			4	Week 13	NC	NC	33000 ± 10400	22200 ± 4800
			4	Week 39	NC	NC	33000 ± 9800	23200 ± 5000
		30	8	Week 1	NC	NC	154000 ± 35000	125000 ± 32000
			8	Week 13	NC	NC	194000 ± 98000	204000 ± 60000
			8	Week 39	NC	NC	137000 ± 109000[d]	190000 ± 58000
	SC	30	8	Week 1	507 ± 101	348 ± 152	123000 ± 21000	81200 ± 18500
			8	Week 13	505 ± 197	582 ± 136	120000 ± 40000	142000 ± 37000
			8	Week 39	432 ± 193	721 ± 179	106000 ± 48000	175000 ± 55000
Pregnant monkeys	IV	0.3	20	Week 1	-	11.7 ± 1.1	-	1480 ± 150[e]
			18	Week 17	-	15.4 ± 3.3	-	2540 ± 520[f]
		3	20	Week 1	-	118 ± 21	-	14100 ± 2600[g]
			16	Week 17	-	135 ± 38	-	21300 ± 5900[h]
		30	28	Week 1	-	1110 ± 200	-	144000 ± 29000[i]
			20	Week 17	-	1220 ± 290	-	185000 ± 24000[j]

Mean ± SD (individual values if n = 2); NC, Not calculated; -, Not applicable

C_{max}, Maximum serum concentration; AUC, Area-under the drug serum concentration-time curve

a) Rabbits, $AUC_{0\text{-}inf}$ on Day 1 after the start of administration and $AUC_{0\text{-}336h}$ on Week 14; monkeys, $AUC_{0\text{-}336h}$

b) n = 3; c) n = 2; d) n = 7; e) n = 19; f) n = 17; g) n = 18; h) n = 12; i) n = 26; j) n = 14

Burosumab (0.3, 3, or 30 mg) was administered intravenously once every 2 weeks to pregnant monkeys (12-26/group) from Gestation Day 20 until delivery. The results showed that the ratio of serum burosumab concentration in fetuses to that in maternal animals (fetus/mother ratio) (mean ± standard deviation [SD]) on Gestation Day 133 in the 30 mg/kg group was 0.25 ± 0.05. $t_{1/2}$ (mean ± SD) calculated from the serum burosumab concentration on Day 5 to Day 63 after birth in the 0.3, 3, and 30 mg/kg groups was 14.6 ± 3.7 to 16.1 ± 4.8 days in maternal animals and 15.2 ± 2.6 to 21.3 ± 2.2 days in pups.

The anti-burosumab antibody was not detected in any of maternal animals in the 0.3 or 3 mg/kg group either during gestation or during lactation, but detected in 2 of 14 maternal animals in the 30 mg/kg group (during lactation). No anti-burosumab antibody was detected in fetuses or pups of any groups.

4.2 Distribution

No distribution study was conducted.

4.3 Metabolism

No metabolic study was conducted.

4.4 Excretion

No excretion study was conducted.

4.R Outline of the review conducted by PMDA

On the basis of the results of the nonclinical pharmacokinetic studies submitted, PMDA concludes that there were no particular problems. Human pharmacokinetics is discussed in Section "6.2 Clinical pharmacology."

5. Toxicity and Outline of the Review Conducted by PMDA

The following toxicity studies were conducted: single-dose toxicity studies, repeated-dose toxicity studies, reproductive and developmental toxicity studies, and other studies (tissue cross-reactivity studies and a 2-week repeated subcutaneous dose study in a mouse model of the disease).

5.1 Single-dose toxicity

Acute toxicity of burosumab was evaluated by a single dose intravenous toxicity study in rabbits and from the results of the first dose in a repeated subcutaneous and intravenous toxicity study in cynomolgus monkeys (Table 10).

Table 10. Outline of single dose toxicity studies

Test system	Route of administration	Dose (mg/kg)	Main findings	Approximate lethal dose (mg/kg)	CTD
Male and female rabbits (NZW)	IV	0,[a] 0.03, 0.3, 3	Death or moribund sacrifice[b] 3 mg/kg (1 of 10 males): weight loss; decrease in locomotor activity; mucous feces; soiled periproctal region; increased urinary phosphate; decreases in urine pH and urinary potassium excretion; urine occult blood; increases in serum total cholesterol, triglycerides, glucose, and creatinine; decreased serum calcium; white substances in endocardium; whitening and hardening of lung; reddening of stomach mucosa and thickening of stomach wall; mineral deposition in multiple organs; intra-atrial thrombus and perivascular edema of heart; alveolar edema and inflammatory cell infiltration of lung; edema of trachea and stomach (mucosa, muscle layers, blood vessels); congestion and bleeding of trachea, stomach, and thymus; enhanced thigh bone resorption, increased osteoclasts, fibrosis of periosteum, bone marrow necrosis, congestion, and bleeding ≥0.03 mg/kg: increased urine protein; decreases in red blood cell count, hematocrit, and hemoglobin concentration; increased serum urea nitrogen ≥0.3 mg/kg: decreased serum creatinine, increases in serum phosphorus and $1,25(OH)_2D$ 3 mg/kg: decreased food consumption; decreases in urine sodium and chloride excretion; increased eosinophil count; increases in serum α-globulin and γ-globulin; decreases in serum ALP, chloride, albumin, albumin/globulin ratio, and glucose; mineral deposition in aorta (tunica media), heart (muscle fibers, blood vessels), kidney (renal corpuscles, renal tubules, blood vessels), lung (bronchi, mucosa, alveoli), and stomach (fundic gland); perivascular fibrosis, tubular dilatation, regeneration, and basophilic change of tubular epithelial cells in kidney; multinucleated giant cells in bronchial mucosa of lung; multinucleated giant cells, mononuclear cell infiltration, and edema of aorta (tunica media)	3	4.2.3.1-1
Male and female cynomolgus monkeys	IV	30	Acute toxicity was evaluated in a 14-week repeated intravenous toxicity study and a 40-week repeated intravenous and subcutaneous toxicity study. Decreased food consumption, increased serum calcium/phosphate/$1,25(OH)_2D$	>30	4.2.3.2-3 4.2.3.2-4
	SC	30	Acute toxicity was evaluated in a 40-week repeated intravenous and subcutaneous toxicity study. Increased serum calcium/phosphate/$1,25(OH)_2D$	>30	4.2.3.2-4

a) 10 mmol/L sodium glutamate, 262 mmol/L D-sorbitol, 0.5 mg/mL polysorbate 80 (pH 5.5)
b) The main cause of the death was considered to be renal failure due to calcinosis of the kidney.

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies were conducted for up to 40 weeks in rabbits and cynomolgus monkeys (Table 11). Main changes were increases in serum phosphorus and $1,25(OH)_2D$ concentrations, ectopic mineral deposition in multiple organs and tissues, degeneration of heart and kidney, and bone hyperplasia.

At the no observed adverse effect level (NOAEL) of 40-week once every 2-week doses in mature cynomolgus monkeys (0.03 mg/kg in males, 0.3 mg/kg in females), C_{max}[7] was 2.24 μg/mL in males and 17.10 μg/mL in females, and $AUC_{0\text{-}336\ h}$ was 376 μg•h/mL in males and 2910 μg•h/mL in females. The observed C_{max} was 0.20 (male) and 1.54 (female) times, and AUC was 0.13 (male) and 1.00 (female) times[8] the exposure[9] following the subcutaneous doses of burosumab at the recommended clinical dose

7) Serum burosumab concentration at 10 minutes after burosumab administration
8) $AUC_{0\text{-}336\ h}$ observed in the study using mature cynomolgus monkeys (administration once every 2 weeks) was multiplied by 2 for comparison with the results obtained with the recommended clinical dosage regimen (administration once every 4 weeks) in order to adjust for the dosing frequency.
9) Mean C_{max} (11.11 μg/mL) and mean AUC_{τ} (5808 μg•h/mL) under the steady state, estimated by Bayesian inference using the population pharmacokinetic analysis (CTD 5.3.3.5-1) based on the serum burosumab concentration following once every 4 week administration of burosumab (1 mg/kg) in Study UX023-CL303 (CTD 5.3.5.1-1 to 2) in adult patients with XLH.

(1 mg/kg once every 4 weeks) in adult patients with XLH. At the NOAEL (0.3 mg/kg) in 40-week administration once every 2 weeks to juvenile cynomolgus monkeys, C_{max} was 12.70 μg/mL and $AUC_{0\text{-}312\,h}$ was 1870 μg•h/mL. The observed C_{max} was 0.59 to 0.78 times, and AUC was 0.29 to 0.38 times the exposure[10] following the recommended clinical dose of subcutaneous burosumab (0.8 mg/kg once every 2 weeks) in pediatric patients (1-12 years old) with XLH.

Table 11. Outline of repeated-dose toxicity studies

Test system	Route of administration	Dosing period	Dose (mg/kg)	Main findings	NOAEL (mg/kg)	CTD
Male and female rabbits (NZW)	IV	14 weeks (once every 2 weeks)	0,[a] 0.03, 0.3, 3	Death or moribund sacrifice[b] 3 mg/kg (1 of 4 males): increases in monocyte count and large unstained cell count; decreased lymphocyte count; increases in serum creatinine phosphokinase, triglycerides, glucose, urea nitrogen, creatinine, β-globulin, and γ-globulin; decreased serum calcium; mineral deposition in lung (bronchial mucosa, bronchioles, alveoli), gastrointestinal tract, spleen, and adrenals; pulmonary congestion, bleeding, alveolar edema, detachment of bronchial epithelium, and infiltration of inflammatory cells; inflammatory cell infiltration and submucosal edema in stomach; periosteal fibrosis and osteoclast growth in femur. ≥0.03 mg/kg: increased serum $1,25(OH)_2D$ ≥0.3 mg/kg: increased serum phosphorus, mineral deposition in kidney (renal tubules)[c] 3 mg/kg: decreases in body weight and food consumption; increased neutrophil count; decreases in hematocrit and hemoglobin concentration; increases in serum total cholesterol and α-globulin; decreases in serum chloride, albumin, and albumin/globulin ratio; white granular change of the surface of aortic intima; mineral deposition in aorta (tunica media), heart (blood vessels, cardiac muscle fibers), and kidney (renal corpuscles, renal tubules, blood vessels); cartilaginous metaplasia, edema, inflammatory cell infiltration (tunica media), and multinucleated giant cells in aorta; inflammatory cell infiltration (blood vessels, tunica media, stroma) and necrosis/degeneration (cardiac muscle fibers) of heart, fibrosis, hyaline casts, and regeneration (renal tubules) in kidney	0.3	4.2.3.2-1
Male and female cynomolgus monkeys	IV	14 weeks (once every 2 weeks) + 6-week recovery period[d]	0,[a] 0.03, 0.3, 3, 30	≥0.03 mg/kg: increased serum $1,25(OH)_2D$ ≥0.3 mg/kg: increased serum phosphorus, decreased serum bALP, mineral deposition in kidney (renal tubules)[c] ≥3 mg/kg: increases in serum calcium, osteocalcin, and CTx; mineral deposition in aorta, brain (meninges), colon, lung (cartilage, mucosa), and pituitary gland; multinucleated cells in renal tubules and urinary tract epithelium of kidney 30 mg/kg: decreased body weight; reduced body weight gain; swollen femur and humerus; increases in urine phosphate concentration and excretion; decreases in hematocrit and hemoglobin concentration; increases in total white blood cell count and neutrophil count; intramuscular mass (multinucleated macrophages and calcified granular substances with fibrous connective tissue); hyperplasia of femoral and humeral periosteum; mineral deposition in adrenals (medulla), bone, brain (meninges, choroid plexus), spinal cord (dura mater), eye (conjunctiva), heart/sciatic nerve, vesicular gland, stomach, tracheal mucosa, urinary bladder, pulmonary artery, and parathyroid gland; renal fibrosis and degeneration and regeneration of renal tubules Reversible (mineral deposition in multiple organs and tissues was observed)	0.3	4.2.3.2-3

[10] Mean C_{max} (16.20 and 21.35 μg/mL, respectively) and mean AUCτ (4896 and 6456 μg•h/mL, respectively) under the steady state, estimated by Bayesian inference using the population pharmacokinetic analysis (CTD 5.3.3.5-1) based on the serum burosumab concentration following once every 2 or 4 week administration of burosumab in Study UX023-CL205 (CTD 5.3.5.2-6) in pediatric patients (1- 4 years old) with XLH and Study UX023-CL201 (CTD 5.3.5.2-5) in pediatric patients (5-12 years old) with XLH.

Table 11. Outline of repeated-dose toxicity studies (continued)

Male and female cynomolgus monkeys	IV	40 weeks (once every 2 weeks) + 13-week recovery period[d)]	0,[f)] 0.03, 0.3, 3, 30	Death or moribund sacrifice[g)] 30 mg/kg (1 of 8 males): lateral position; increases in urine protein and glucose concentration ≥0.03 mg/kg: increases in serum phosphorus and $1,25(OH)_2D$ ≥0.3 mg/kg: increases in serum osteocalcin and CTx; opaque white mass around the surface of bones of limbs (males); mineral deposition in subcutaneous tissue, muscles, and connective tissue of joint capsules (males) ≥3 mg/kg: swelling of limbs; decreases in hematocrit and hemoglobin concentration; increased platelet count, mineral deposition in lung, testis (rete testis, seminiferous tubules), trachea and kidney; renal degeneration/necrosis, regeneration (renal tubules), and fibrosis (interstitium); increase and multinucleation (epithelium); basophilic change of lung and trachea (perichondrial cells) 30 mg/kg: abnormal gait; decreases in body weight and food consumption; increased heart rate; decreased ST; decreases in left ventricle end-diastolic and end-systolic volume, stroke volume, and ejection fraction; increased urinary phosphate excretion; decreases in red blood cell count, MCV, MCH, and lymphocyte count; increases in neutrophil count and fibrinogen; prolonged PT and APTT; decreased nucleated cells in bone marrow; decreases in serum albumin, total protein, albumin/globulin ratio, creatinine, and chloride; decreased serum bALP[h)]; increases in serum ALP, urea nitrogen, β-globulin, and calcium; increases in range, thickness, volume, and density of cortical bone; increases in total bone density, osteoid volume, and osteoid surface; opaque white mass in subcutaneous tissue, around bone surface, and within skeletal muscles; hypertrophy and protrusion of bones; rough bone surface; deposition of white matters to aorta; increased weight of kidney and adrenal; mineral deposition in aorta, eyes (corneal margin, conjunctiva), heart, kidney (loop of Henle, collecting duct), liver (blood vessels), lung (bronchi, alveoli), sciatic nerve, skeletal muscles, spinal cord, and stomach (blood vessels, fundic gland); basophilic change of bones (femur, sternum); decreased trabecular bone mass (femur, sternum); dilated Haversian canal in cortical bone; spongiotic hyperplasia of cortical bone[i)]; infiltration of inflammatory cells into renal tubules and papilla/cortex of kidney Reversible (no clear reversibility could be confirmed by quantitative computed tomographic analysis of cortical bone, cardiac function, and peripheral bones, and in change in bone strength or in histopathological changes of long bones, heart, kidneys, etc.)	0.03/0.3 (male/female)	4.2.3.2-4
	SC		30	Observed changes were similar to those in the 30 mg/kg i.v. group.		
Male and female juvenile cynomolgus monkeys	IV	40 weeks (once every 2 weeks) + 13-week recovery period[j)]	0,[f)] 0.03, 0.3, 3	≥0.03 mg/kg: increased serum $1,25(OH)_2D$ and CTx, increased total bone density ≥0.3 mg/kg: increases in urine calcium/creatinine ratio and calcium excretion; decreases in serum ALP and bALP; increases in serum phosphorus and osteocalcin; increased cortical bone density 3 mg/kg: swollen fingers and toes/feet; opaque white mass in subcutaneous tissue; mineral deposition in subcutaneous tissue and muscle connective tissue; increases in urine creatinine, sodium, potassium, and chloride excretion; accumulated substances in long bone; increases in bone resorption, osteoclasts, and osteoblasts in femur; mineral deposition in eyes (corneal margin, conjunctiva), kidney (renal tubules), lung, skeletal muscles, submandibular gland, and extremities. Reversible (mineral deposition in kidney/eyes was detected)	0.3	4.2.3.2-5
	SC		3	Observed changes were similar to those in the 3 mg/kg i.v. group.		

a) 10 mmol/L sodium glutamate, 262 mmol/L D-sorbitol, 0.5 mg/mL polysorbate 80 (pH 5.5)
b) The main cause of the death was renal failure due to calcinosis of the kidney.
c) The change was extremely slight, and the severity and extent of the lesion were different from those in the 3 mg/kg group, from which it was concluded that the change was not caused by burosumab.

d) Studied in animals of the control group and 30 mg/kg group.
e) The severity of the change was not different from that observed in the control group, from which it was determined that the change was spontaneous.
f) 10 mmol/L L-Histidine, 252 mmol/L D-sorbitol, 0.5 mg/mL polysorbate 80, 10 mmol/L L-methionine (pH 6.25)
g) The animal showed abnormal gait and lateral position due to the swelling of the limbs caused by ectopic mineral deposition severer than in other animals, and was therefore euthanized.
h) One male in the 30 mg/kg s.c. group showed increased serum bALP, which was considered due to the sex difference in bone metabolic cycle.
i) Increased thickness and density in cortical bones were observed in females of the 30 mg/kg group, while decreased density in cortical bones was observed in some males of the 30 mg/kg group. The difference was considered due to the sex difference in bone metabolic cycle.
j) Studied in animals of the control group and 3 mg/kg group

5.3 Genotoxicity

Burosumab is a human IgG1 monoclonal antibody and is unlikely to directly act on DNA or other components of chromosomes. Therefore, no genotoxicity study was conducted.

5.4 Carcinogenicity

Burosumab does not bind to FGF23 of rodents, no carcinogenicity study was conducted in rodents.

The applicant's explanation explained about the carcinogenicity of burosumab:
There are no reports that show an association of the FGF23-inhibiting effect with tumorigenicity, or there are no reports of proliferative disorders either in patients with hyperphosphatemic familial tumoural calcinosis or in FGF23 knockout mice. In addition, no proliferative change was observed in an *ex vivo* assay using T cells isolated from FGF23 knockout mice. Furthermore, there were no findings suggestive of an association between burosumab and tumorigenicity either in the general toxicity studies or genotoxicity studies of burosumab. Increased osteoclasts and osteoblasts were observed in some animals in the general toxicity studies of burosumab. However, they are correlated with increased serum phosphorus concentration, and serum phosphorus concentration is maintained within the normal range by monitoring in the clinical setting. Given these, increased osteoclasts and osteoblasts are not considered indicative of a risk of carcinogenicity. The carcinogenic risk of burosumab is thus minimal.

5.5 Reproductive and developmental toxicity

Because burosumab does not bind to FGF23 of rodents, studies on embryo-fetal development and for effects on pre- and postnatal development were conducted in cynomolgus monkeys. The results showed increases in abortion and embryonic/fetal mortality, increased preterm deliveries, and decreased mean gestation period (Table 12). For mineral deposition in the placenta presumably caused by the excessive pharmacological action of burosumab, the applicant pointed out the possibility that these findings are the manifestations of mineral deposition observed in the placenta. C_{max} (135 μg/mL) and $AUC_{0\text{-}336\ h}$ (21300 μg•h/mL) at the NOAEL in embryos/fetuses (3 mg/kg) were 12.1 and 7.3[11)] times, respectively, the exposure[9)] to burosumab administered subcutaneously at the recommended clinical dose (1 mg/kg once every 4 weeks) in adult patients with XLH.

11) $AUC_{0\text{-}336\ h}$ observed in the study using pregnant cynomolgus monkeys (administration once every 2 weeks) was multiplied by 2 for comparison with the results obtained with the recommended clinical dosage (administration once every 4 weeks) in order to adjust for the dosing frequency.

Table 12. Outline of reproductive and developmental toxicity study

Type of study	Test system	Route of administration	Dosing period	Dose (mg/kg)	Main findings	NOAEL (mg/kg)	CTD
Study of embryo-fetal development, study of effects on pre- and postnatal development	Cynomolgus monkeys	IV	Gestation Day 20 to delivery (once every 2 weeks)	0,[a] 0.3, 3, 30	Maternal animals[b]: ≥0.3 mg/kg: increases in total urine phosphate, calcium excretion, and calcium/creatinine ratio; increases in serum phosphorus, $1,25(OH)_2D$, and osteocalcin 3 mg/kg: increased premature delivery rate ≥3 mg/kg: decreases in serum ALP and bALP; mineral deposition in heart (aortic tunica media), ovary (ovarian follicles), and uterus (uterine gland, blood vessels); basophilic change in tracheal perichondrial cells and bronchial cartilage; decreased gestation period 30 mg/kg: decreases in hematocrit, hemoglobin concentration, MCV, and MCH; increased serum calcium; increased frequency and extent of urine phosphate crystals; increased serum CTx; increases in total bone content and density due to increased cortical bones; mineral deposition in kidney (loop of Henle, collecting duct), lung (bronchus, alveoli), aorta, sciatic nerve, mammary gland, and pituitary gland; basophilic change of pulmonary perichondrial cells and bronchial cartilage; increases in abortion and postimplantation mortality of embryos/fetuses Fetuses[c]: 30 mg/kg: increased placental weight; mineral deposition in placenta; minerals in pulmonary alveolar space[d]; decreases in red blood cell count, hematocrit, hemoglobin concentration, MCV, lymphocyte count, and lymphocyte ratio; increases in eosinophil count and eosinophil ratio; increased serum phosphorus; decreased serum bALP, increased cortical bone density Offspring[e]: 30 mg/kg: increased serum phosphorus	Maternal animals: 0.3 Fetuses/embryos and pre-and postnatal development: 3	4.2.3.5.3-1

a) 10 mmol/L L-histidine, 252 mmol/L D-sorbitol, 0.5 mg/mL polysorbate 80, 10 mmol/L L-methionine (pH 6.25)
b) The effect of burosumab on maternal animals in the control group and 30 mg/kg group was evaluated on Gestation Day 133 and at the end of lactation period.
c) The effect of burosumab on fetuses in the control group and 30 mg/kg group was evaluated on Gestation Day 133.
d) No mineral deposition was observed.
e) The effect of burosumab on offsprings in each dose group was evaluated at the end of the lactation period.

5.6 Other studies

5.6.1 Tissue cross-reactivity

A tissue cross-reactivity study was conducted using normal tissues of humans, rabbits, and cynomolgus monkeys (Table 13). The results showed no cross-reactivity in normal tissues of humans, rabbits, or cynomolgus monkeys, based on which the applicant explained that burosumab is unlikely to exhibit toxicity by directly binding to normal tissues.

Table 13. Outline of tissue cross-reactivity study

Test system	Method	Main findings	CTD
Normal tissues of humans, rabbits, and cynomolgus monkeys	Immunohistochemical staining	No cross-reactivity was observed in normal tissues of humans, rabbits, and cynomolgus monkeys.	4.2.3.7.7-1

5.6.2 Effect of anti-FGF23 antibody in wild type mice and hypophosphatemic mice

A subcutaneous administration study was conducted using Hyp mice to evaluate the anti-FGF23 antibody in patients with FGF23-related hypophosphatemic rickets/osteomalacia (Table 14). Plasma phosphate concentration and the incidence and severity of ectopic mineral deposition caused by anti-FGF23 antibody were lower in Hyp mice than in WT mice. The applicant explained that the risk of hyperphosphatemia and ectopic mineral deposition is low in patients with hypophosphatemia.

Table 14. Outline of the effect of anti-FGF23 antibody in WT and Hyp mice

Test system	Method	Main findings	CTD
WT and Hyp mice	Murine anti-FGF23 antibody (0,[a] 3, 10, or 30 mg/kg) was administered subcutaneously twice weekly for 2 weeks to WT and Hyp mice, and blood phosphate concentration, $1,25(OH)_2D$ concentration, and mineral deposition in organs and tissues were evaluated.	The maximum plasma phosphate concentration was lower in Hyp mice than in WT mice. The $1,25(OH)_2D$ concentration was higher in the murine anti-FGF23 antibody group of Hyp mice than in the murine anti-FGF23 antibody group of WT mice. Mineral deposition was observed in the kidney, lung, heart, aortic arch, and thoracic aorta in WT mice and in the kidney and lung in Hyp mice.	Reference data 4.2.3.7.7-2

a) 8 g/L sodium chloride, 200 mg/L potassium chloride, 1.15 g/L disodium hydrogenphosphate, 200 mg/L potassium dihydrogenphosphate (pH 7.4)

5.R Outline of the Review Conducted by PMDA

5.R.1 Toxicity profile of burosumab

The applicant's explanation about the toxicity profile of burosumab and the presumed risk in its clinical use:

The main toxicities of burosumab observed in the nonclinical toxicity studies were ectopic mineral deposition and hyperosteogeny in multiple tissues presumably caused by increased serum phosphorus and $1,25(OH)_2D$ concentration due to the pharmacological action of burosumab. FGF23 is not present in excess in normal animals, and it is likely that the pharmacological action of burosumab[12)] was excessively intense in the nonclinical studies using normal mice, rabbits, and cynomolgus monkeys. The risk of ectopic mineral deposition was evaluated based on the results of the clinical and nonclinical studies on burosumab. Results suggested that ectopic mineral deposition is induced when serum phosphorus concentration exceeds the physiological range. Serum phosphorus concentration is considered a direct biochemical marker for possible ectopic mineral deposition induced by burosumab, the risk of mineral deposition may be reduced if serum phosphorus concentration is controlled within the age-adjusted normal range in clinical use.

PMDA accepted the applicant's explanation. Safety of burosumab in humans, including heterotopic calcification, is discussed in Section "7.R.4 Safety."

12) Murine anti-FGF23 antibody was used in mice.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

Table 15 shows the formulations used in the clinical studies. Although the manufacturing processes of the drug substance and the drug product were changed during the development, the comparability of the quality attributes of the drug substance and drug product between before and after the process change was evaluated and confirmed [see Sections "2.1.4 Manufacturing process development" and "2.2.3 Manufacturing process development"]. The proposed commercial formulations are 10, 20, and 30 mg/mL formulations manufactured using the drug substance prepared by the proposed manufacturing method. The proposed commercial formulations were used in the phase II study, the Japanese phase III study, and the global phase III study.

Table 15. Formulations used in clinical studies

Drug substance	Formulations	Formulations concentration (mg/mL)	Development phase (study identifier)	
			Japanese studies (including global studies in which Japanese medical institutions participated)	Foreign studies
Method A	Method 1	2	-	Phase I study (Study KRN23-US-02)
Method B	Method 2	2, 10	-	Phase I study (Study KRN23-US-02) Phase I/II studies (Studies KRN23-INT-001 and KRN23-INT-002)
Method C	Method 3	2, 10, 30	Phase I study (Study KRN23-001[a)]) Phase II study (Study KRN23-002[a)]) Phase III studies (Studies UX023-CL301,[a)] UX023-CL303,[a)] and UX023-CL304[a)])	Phase I/II study (Study KRN23-INT-002) Phase II studies (Studies UX023-CL201, UX023-CL203, UX023-CL205, and UX023T-CL201)
Proposed method	Proposed method	10, 20, 30	Phase II study (Study KRN23-002[a)]) Phase III studies (Studies KRN23-003 and UX023-CL301[a)])	Phase II study (Study UX023T-CL201)

-: Not applicable
a) Global study

Serum burosumab concentration was measured by ELISA or ECL. The lower limit of quantitation was 50 ng/mL with ELISA and 36 or 50 ng/mL with ECL. The anti-burosumab antibody was measured by ELISA or ECL, and neutralizing antibody was measured by ECL.

6.2 Clinical pharmacology

The applicant submitted the data from 7 clinical studies (Studies KRN23-001, KRN23-002, KRN23-003, KRN23-US-02, UX023-CL301, UX023-CL303, and UX023-CL304) and the results of the population pharmacokinetic analysis as the evaluation data. The applicant also submitted the data from 1 foreign clinical study (Study UX023T-CL201) as the reference data. The main results of the studies are described below.

6.2.1 Studies in adult patients with XLH

6.2.1.1 Global phase I study (CTD 5.3.4.2-1, Study KRN23-001 [July 2014 to June 2015])

An open-label, dose escalation study was conducted in Japanese and non-Japanese[13)] adult patients with XLH (target sample size; 15 subjects, 5/group) to investigate the pharmacokinetics, pharmacodynamics, and safety of burosumab following a single subcutaneous dose.

13) Korea

The main inclusion criteria were adult patients with XLH with serum FGF concentration of ≥30 pg/mL at the pre-treatment test. The main exclusion criteria were patients who took vitamin D, its metabolites, or related drugs within 21 days before the pre-treatment test or after, and patients who took a phosphate preparation for the treatment of XLH within 10 days before, or after, the pre-treatment test.

A single dose of burosumab (0.3, 0.6, or 1 mg/kg) was administered subcutaneously to patients in each cohort (Cohort 1, 2, or 3).

All 18 patients who received burosumab were included in the population for the analysis of pharmacokinetics, pharmacodynamics, and safety.

Table 16 shows the pharmacokinetic parameters following a single subcutaneous dose of burosumab.

Table 16. Pharmacokinetic parameters of a single subcutaneous dose of burosumab

Dose (mg/kg)	Patients	n	C_{max} (μg/mL)	$AUC_{0-\infty}$ (μg▪h/mL)	t_{max} (h)	$t_{1/2}$ (h)	CL/F (mL/h/kg)	V_z/F (mL/kg)
0.3	Entire population	6	1.71 ± 0.51	1180 ± 370[a)]	166 [46.5, 168]	289 ± 121[a)]	0.277 ± 0.096[a)]	107 ± 38[a)]
	Japanese	3	1.77 ± 0.22	1180 ± 500	167 [46.5, 168]	295 ± 140	0.291 ± 0.129	107 ± 18
	Korean	3	1.65 ± 0.77	1040, 1340[b)]	166 [95.9, 166]	180, 378[b)]	0.223, 0.290[b)]	57.9, 158[b)]
0.6	Entire population	5	2.95 ± 0.67	2220 ± 920	167 [165, 334]	315 ± 131	0.309 ± 0.123	122 ± 8
	Japanese	3	3.13 ± 0.84	2370 ± 1160	167 [166, 167]	340 ± 154	0.299 ± 0.150	125 ± 4
	Korean	2	2.41, 2.93	1460, 2510	165, 334	186, 370	0.239, 0.410	110, 127
1	Entire population	7	5.19 ± 2.12	3770 ± 1670	166 [93.5, 168]	336 ± 85	0.307 ± 0.116	143 ± 49
	Japanese	4	5.41 ± 2.07	4040 ± 1950	131 [93.5, 167]	342 ± 115	0.292 ± 0.130	134 ± 47
	Korean	3	4.91 ± 2.62	3420 ± 1530	166 [94.2, 168]	327 ± 40	0.328 ± 0.118	155 ± 60

Mean ± SD (individual values if n = 2), t_{max} is expressed in median [range].
C_{max}, Maximum serum concentration; $AUC_{0-\infty}$, Area under serum concentration-time curve from time 0 to infinity; t_{max}, Time to maximum serum concentration; $t_{1/2}$, Elimination half-life; CL/F, Apparent total clearance; V_z/F, Apparent distribution volume
a) n = 5
b) n = 2

Table 17 shows serum phosphorus concentration over time, a parameter of the pharmacodynamic effect.

Table 17. Change in serum phosphorus concentration over time following a single subcutaneous dose of burosumab

Dose (mg/kg)	Patients	n	Baseline	Day 2	Day 3	Day 5	Day 8	Day 15	Day 22	Day 29	Day 36	Day 50
0.3	Entire population	6	1.80 ± 0.24	1.98 ± 0.29	2.17 ± 0.46	2.57 ± 0.31	2.55 ± 0.29	2.52 ± 0.53	2.25 ± 0.36	2.12 ± 0.48	2.05 ± 0.38	1.90 ± 0.24
	Japanese	3	1.80 ± 0.10	2.13 ± 0.21	2.40 ± 0.53	2.70 ± 0.36	2.73 ± 0.31	2.63 ± 0.74	2.37 ± 0.49	2.27 ± 0.51	2.23 ± 0.12	2.03 ± 0.15
	Korean	3	1.80 ± 0.36	1.83 ± 0.31	1.93 ± 0.29	2.43 ± 0.25	2.37 ± 0.12	2.40 ± 0.36	2.13 ± 0.21	1.97 ± 0.50	1.87 ± 0.49	1.77 ± 0.25
0.6	Entire population	5	1.92 ± 0.38	2.02 ± 0.41	2.30 ± 0.50	2.52 ± 0.65	2.82 ± 0.61	2.86 ± 0.85	2.38 ± 0.74	2.34 ± 0.75	2.18 ± 0.43	1.90 ± 0.43
	Japanese	3	2.17 ± 0.21	2.20 ± 0.44	2.57 ± 0.38	2.83 ± 0.51	3.10 ± 0.44	3.27 ± 0.64	2.73 ± 0.45	2.70 ± 0.62	2.27 ± 0.47	2.00 ± 0.36
	Korean	2	1.4, 1.7	1.6, 1.9	1.6, 2.2	1.6, 2.5	1.9, 2.9	1.6, 2.9	1.2, 2.5	1.3, 2.3	1.7, 2.4	1.3, 2.2
1	Entire population	7	1.63 ± 0.40	2.00 ± 0.46	2.14 ± 0.50	2.40 ± 0.57	2.40 ± 0.42	2.66 ± 0.63	2.44 ± 0.52	2.17 ± 0.54	1.99 ± 0.56	1.71 ± 0.38
	Japanese	4	1.70 ± 0.32	2.15 ± 0.26	2.28 ± 0.32	2.60 ± 0.43	2.55 ± 0.17	2.80 ± 0.22	2.48 ± 0.31	2.20 ± 0.34	2.10 ± 0.48	1.80 ± 0.35
	Korean	3	1.53 ± 0.55	1.80 ± 0.66	1.97 ± 0.71	2.13 ± 0.70	2.20 ± 0.61	2.47 ± 1.01	2.40 ± 0.82	2.13 ± 0.83	1.83 ± 0.72	1.60 ± 0.46

Mean ± SD (individual values for n = 2); Unit, mg/dL

Anti-burosumab antibody formation was investigated at 2 time points; before the dose of burosumab and on Day 50. The anti-burosumab antibody was detected at both time points in 1 patient (Japanese) in the 0.3 mg/kg group, but no neutralizing antibody was detected.

Adverse events and adverse drug reactions were observed in 66.7% (4 of 6) of patients and 50.0% (3 of 6) of patients, respectively, in the 0.3 mg/kg group, 80.0% (4 of 5) of patients and 0% (0 of 5) of patients, respectively, in the 0.6 mg/kg group, and 85.7% (6 of 7) of patients and 28.6% (2 of 7) of patients, respectively, in the 1 mg/kg group. There was no death, serious adverse event, or adverse event leading to treatment discontinuation.

Increases in laboratory values related to the pharmacodynamic effect of burosumab were observed, while no other clinically significant changes in were observed laboratory values. Among adverse events related to laboratory values, a causal relationship to burosumab could not be ruled out for abnormal white blood cell count in 1 patient in the 0.3 mg/kg group. However, the event was mild and resolved without any intervening treatment.

Vital signs and electrocardiogram did not show any clinically significant changes.

6.2.1.2 Foreign phase I study (CTD 5.3.4.2-2, Study KRN23-US-02 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A placebo-controlled, randomized, double-blind, dose escalation study in non-Japanese[14)] adult patients with XLH (maximum target sample size, 40 subjects) was conducted to investigate the pharmacokinetics, pharmacodynamics, and safety of burosumab following a single intravenous or subcutaneous dose.

The main inclusion criteria were adult patients with XLH with serum FGF concentration of >30 pg/mL at the pre-treatment test. The main exclusion criteria were patients who took vitamin D, its metabolites,

14) US

related drugs, or a phosphate preparation within 10 days before the pre-treatment test or during the treatment.

In the intravenous administration cohort, placebo or burosumab (0.003, 0.01, 0.03, 0.1, or 0.3 mg/kg) was administered as a single dose intravenously and, in the subcutaneous administration cohort, placebo or burosumab (0.1, 0.3, 0.6, or 1 mg/kg) was administered as a single dose subcutaneously.

All 38 patients who were randomized and received the study drug (22 receiving an intravenous dose [5 in the placebo group, 17 in the burosumab group], 16 receiving a subcutaneous dose [4 in the placebo group, 12 in the burosumab group]) were included in the safety analysis population, and all 29 patients who received burosumab were included in the population for pharmacokinetic analysis.

Table 18 shows the pharmacokinetic parameters following a single intravenous or subcutaneous dose of burosumab administration. The absolute bioavailability (BA) (calculated as the arithmetic mean ratio of $AUC_{0-\infty}$ [subcutaneous administration/intravenous administration]) was 90% and 128%, respectively, at 0.1 mg/kg and 0.3 mg/kg.

Table 18. Pharmacokinetic parameters of a single dose of burosumab

Route of administration	Dose (mg/kg)	n	C_{max} (μg/mL)	$AUC_{0-\infty}$ (μg・h/mL)	t_{max} (h)	$t_{1/2}$ (h)
IV	0.003	3	0.0693 ± 0.00712	NC	2.17 [1.17, 2.17]	NC
	0.01	3	0.256 ± 0.016	52.0 ± 15.3	1.17 [1.17, 2.17]	199 ± 83.9
	0.03	3	1.04 ± 0.202	156 ± 28.7	1.17 [0.230, 2.17]	180 ± 98.8
	0.1	5	2.95 ± 0.927	666 ± 144	1.17 [0.170, 2.25]	296 ± 65.9
	0.3	3	9.20 ± 1.83	2170 ± 312	1.18 [1.17, 1.23]	273 ± 29.1
SC	0.1	3	0.755 ± 0.266	599 ± 157	311 [167, 336]	423 ± 119
	0.3	3	3.00 ± 1.01	2400, 3150[a)]	168 [96.0, 311]	304, 420[a)]
	0.6	3	3.62 ± 1.94	3180 ± 1680	239 [167, 241]	322 ± 40.8
	1	3	7.71 ± 2.07	6590, 7210[a)]	242 [167, 409]	296, 601[a)]

Mean ± SD (individual values if n = 2), t_{max} is expressed in median [range]; NC, Not calculable
C_{max}, Maximum serum concentration; $AUC_{0-\infty}$, Area under serum concentration-time curve from time 0 to infinity; t_{max}, Time to maximum serum concentration; $t_{1/2}$, Elimination half-life
a) n = 2

Table 19 shows changes in serum phosphorus concentration over time, a parameter for pharmacodynamic action of burosumab. Burosumab is intended for subcutaneous administration, and thus the results refer to subcutaneous administration only.

Table 19. Changes in serum phosphorus concentration over time following a single subcutaneous dose of burosumab

Dose (mg/kg)	n	Baseline	2 hours post-dose	4 hours post-dose	8 hours post-dose	12 hours post-dose	Day 2	Day 3	Day 4	Day 5
0.1	3	2.17 ± 0.51	2.00 ± 0.66	2.03 ± 0.60	2.07 ± 0.25	1.87 ± 0.23	2.10 ± 0.36	2.43 ± 0.31	2.57 ± 0.21	2.37 ± 0.15
0.3	3	1.87 ± 0.42	1.60 ± 0.27	1.73 ± 0.21	2.00 ± 0.20	2.00 ± 0.10	1.97 ± 0.45	2.53 ± 0.55	2.67 ± 0.45	2.73 ± 0.40
0.6	3	1.90 ± 0.76	1.43 ± 0.21	2.03 ± 0.64	2.30 ± 0.56	2.13 ± 0.67	2.13 ± 0.83	2.43 ± 0.99	2.77 ± 0.76	2.77 ± 0.93
1	3	1.80 ± 0.10	1.67 ± 0.15	2.30 ± 0.60	2.33 ± 0.45	2.00 ± 0.53	2.03 ± 0.21	2.53 ± 0.29	2.97 ± 0.23	2.70 ± 0.52

Dose (mg/kg)	N	Day 8	Day 12	Day 15	Day 18	Day 22	Day 29	Day 36	Day 50
0.1	3	2.97 ± 0.35	-	2.53 ± 0.35	-	2.50 ± 0.20	2.10 ± 0.46	-	1.90 ± 0.35
0.3	3	2.83 ± 0.31	-	2.87 ± 0.29	-	2.67 ± 0.38	2.37 ± 0.12	-	2.07 ± 0.35
0.6	3	3.53 ± 0.40	3.90 ± 1.18	3.37 ± 0.64	3.37 ± 1.12	3.30 ± 0.79	3.00 ± 0.53	2.97 ± 0.64	2.17 ± 0.15
1	3	3.23 ± 0.35	3.07 ± 0.31	3.43 ± 0.12	3.37 ± 0.31	3.43 ± 0.42	3.27 ± 0.06	2.93 ± 0.21	2.20 ± 0.27

Mean ± SD; Unit, mg/dL; -, Not measured

The anti-burosumab antibody was not detected in any of the patients during the period from baseline before the administration of study drug up to Day 50.

After the intravenous dose, adverse events and adverse drug reactions were observed in 2 of 5 patients and 0 of 5 patients, respectively, in the placebo group, 3 of 3 patients and 1 of 3 patients, respectively, in the 0.003 mg/kg group, 3 of 3 patients and 0 of 3 patients, respectively, in the 0.01 mg/kg group, 2 of 3 patients and 1 of 3 patients, respectively, in the 0.03 mg/kg group, 4 of 5 patients and 1 of 5 patients, respectively, in the 0.1 mg/kg group, 2 of 3 patients and 1 of 3 patients, respectively, in the 0.3 mg/kg group. after the subcutaneous dose, adverse events and adverse drug reactions were observed in 2 of 4 patients and 0 of 4 patients, respectively, in the placebo group, 3 of 3 patients and 0 of 3 patients, respectively, in the 0.1 mg/kg group, 2 of 3 patients and 1 of 3 patients, respectively, in the 0.3 mg/kg group, 2 of 3 patients and 1 of 3 patients, respectively, in the 0.6 mg/kg group, and 3 of 3 patients and 0 of 3 patients, respectively, in the 1 mg/kg group. There was no death, serious adverse event, or adverse event leading to treatment discontinuation.

Laboratory values, electrocardiogram, and vital signs did not show any clinically significant changes.

6.2.1.3 Global phase III study (CTD 5.3.5.1-1 and 5.3.5.1-2, Study UX023-CL303 [ongoing since October 2015 (data cut-off June 2017)])

A placebo-controlled, randomized, double-blind, parallel-group study with a continued open-label administration was conducted in Japanese and non-Japanese adult patients with XLH (target sample size; 120 subjects, 60/group) to investigate the efficacy, safety, and pharmacokinetics of burosumab [for

the details of the study design and the results of efficacy and safety study, see Section "7.3.1 Placebo-controlled, double-blind study in adult patients with XLH"].

Table 20 shows changes in trough serum burosumab concentration over time following multiple subcutaneous doses of burosumab (1 mg/kg) once every 4 weeks.

Table 20. Changes in trough serum burosumab concentration following multiple subcutaneous doses of burosumab (1 mg/kg) once every 4 weeks

Placebo[a)]		Burosumab			
Week 36	Week 48	Week 4	Week 24	Week 36	Week 48
6.53 ± 2.70 (n = 12)	5.99 ± 2.97 (n = 66)	3.80 ± 1.62 (n = 68)	5.83 ± 3.43 (n = 68)	8.10 ± 3.18 (n = 16)	5.39 ± 2.88 (n = 62)

Mean ± SD (number of patients); Unit, μg/mL
a) In the placebo group in which burosumab was administered once every 4 weeks from Week 24, serum burosumab concentration was measured from Week 36.

Table 21 shows changes in serum phosphorus concentration over time, a parameter of the pharmacodynamic effect of burosumab.

Table 21. Changes in serum phosphorus concentration[a)] over time following multiple subcutaneous doses of burosumab (1 mg/kg) once every 4 weeks

	Baseline	Week 4	Week 12	Week 20	Week 24	Week 28	Week 36	Week 48
Placebo[b)]	1.92 ± 0.32 (n = 66)	2.02 ± 0.38 (n = 65)	2.06 ± 0.36 (n = 64)	2.06 ± 0.39 (n = 65)	2.07 ± 0.34 (n = 66)	2.95 ± 0.61 (n = 66)	2.60 ± 0.54 (n = 66)	2.47 ± 0.49 (n = 66)
Burosumab	2.03 ± 0.30 (n = 68)	2.99 ± 0.64 (n = 67)	2.69 ± 0.57 (n = 67)	2.70 ± 0.48 (n = 65)	2.53 ± 0.45 (n = 68)	2.69 ± 0.51 (n = 67)	2.54 ± 0.48 (n = 64)	2.47 ± 0.46 (n = 63)

Mean ± SD (number of patients); Unit, mg/dL
a) Value measured under fasting conditions (fasted for ≥8 hours) before burosumab administration
b) In the placebo group, burosumab was administered once every 4 weeks after Week 24.

Formation of the anti-burosumab antibody was investigated from baseline before burosumab administration until Week 24. There was no patient who was positive for the anti-burosumab antibody.

6.2.1.4 Global phase III study (CTD 5.3.5.2-4, Study UX023-CL304 [ongoing since December 2015 (data cut-off August 2017)])

An open-label, uncontrolled study in Japanese and non-Japanese adult patients with XLH (target sample size, 14 subjects) was conducted to investigate the efficacy, safety, and pharmacokinetics of burosumab [for the details of the study design and results of the efficacy and safety studies, see Section "7.3.2 Open-label study on the effect on osteomalacia in adult patients with XLH"].

The trough serum burosumab concentration (mean ± SD [number of patients]) in multiple subcutaneous administration of burosumab (1 mg/kg) once every 4 weeks was 3.96 ± 1.61 μg/mL (14 patients) at Week 4, 5.15 ± 2.89 μg/mL (14 patients) at Week 24, and 5.13 ± 1.89 μg/mL (13 patients) at Week 48.

Table 22 shows the changes in serum phosphorus concentration over time, a parameter of the pharmacodynamic effect of burosumab, following multiple subcutaneous doses of burosumab (1 mg/kg) once every 4 weeks.

Table 22. Changes in serum phosphorus concentration[a)] over time in multiple subcutaneous doses of burosumab (1 mg/kg) once every 4 weeks

Baseline	Week 4	Week 12	Week 20	Week 24	Week 28	Week 36	Week 48
2.24 ± 0.40 (n = 14)	2.87 ± 0.43 (n = 14)	2.72 ± 0.33 (n = 14)	2.61 ± 0.31 (n = 14)	2.60 ± 0.33 (n = 14)	2.60 ± 0.41 (n = 14)	2.47 ± 0.31 (n = 13)	2.43 ± 0.30 (n = 13)

Mean ± SD (number of patients); Unit, mg/dL
a) Values obtained under fasting conditions (fasted for ≥8 hours) before burosumab administration

Formation of the anti-burosumab antibody was investigated from baseline through Week 48. The anti-burosumab antibody was positive at baseline in 4 of 14 patients but, after burosumab administration, there were no patients positive for the anti-burosumab antibody.

6.2.2 Studies in pediatric patients with XLH

6.2.2.1 Japanese phase III study (CTD 5.3.5.2-7, Study KRN23-003 [ongoing since July 2017 (data cut-off June 2018)])

An open-label, uncontrolled study in Japanese patients aged 1 to 12 years with XLH (target sample size, ≥10 subjects) was conducted to investigate the efficacy, safety, and pharmacokinetics of burosumab [for the details of the study design and results of the efficacy and safety study, see Section "7.3.4 Open-label study in Japanese pediatric patients with XLH"].

Table 23 shows changes in trough serum burosumab concentration in multiple subcutaneous administration[15)] of burosumab once every 2 weeks.

Table 23. Changes in trough serum burosumab concentration following multiple subcutaneous doses of burosumab once every 2 weeks

Week 2	Week 4	Week 8	Week 16	Week 24	Week 32	Week 40
3.93 ± 0.84 (n = 15)	6.38 ± 1.34 (n = 15)	8.49 ± 1.92 (n = 15)	8.53 ± 2.50 (n = 15)	11.05 ± 4.54 (n = 15)	11.63 ± 5.15 (n = 15)	11.65 ± 4.61 (n = 15)

Mean ± SD (number of patients); Unit, μg/mL

Table 24 shows changes in serum phosphorus concentration over time, a parameter of the pharmacodynamic effect of burosumab.

Table 24. Changes in serum phosphorus concentration[a)] over time following multiple subcutaneous doses of burosumab once every 2 weeks

Baseline	Week 1	Week 2	Week 4	Week 8	Week 12	Week 16
2.61 ± 0.32 (n = 15)	3.67 ± 0.48 (n = 15)	3.62 ± 0.52 (n = 15)	3.73 ± 0.54 (n = 15)	3.63 ± 0.43 (n = 15)	3.51 ± 0.52 (n = 15)	3.48 ± 0.53 (n = 15)
Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	
3.28 ± 0.62 (n = 15)	3.41 ± 0.48 (n = 15)	3.50 ± 0.46 (n = 15)	3.53 ± 0.43 (n = 15)	3.47 ± 0.35 (n = 15)	3.51 ± 0.45 (n = 15)	

Mean ± SD (number of patients): Unit, mg/dL
a) Value obtained under fasting conditions (fasted for ≥4 hours)

The formation of the anti-burosumab antibody was investigated from baseline before burosumab administration until Week 40. The anti-burosumab antibody was detected in 1 of 15 patients. Neutralizing antibody was negative in this patient.

15) Burosumab (0.8 mg/kg) was administered subcutaneously once every 2 weeks. From Week 6, the dose could be increased to 1.2 mg/kg if the patient met the criteria for a dose increase based on serum phosphate concentration.

6.2.2.2 Global phase III study (CTD 5.3.5.1-3, Study UX023-CL301 [ongoing since September 2016 (data cut-off July 2018)])

A randomized, open-label, parallel-group study in Japanese and non-Japanese patients aged 1 to 12 years with XLH (target sample size; 60 subjects, 30/group) was conducted using oral phosphate and active vitamin D as the controls to investigate the efficacy, safety, pharmacokinetics of burosumab [for the details of the study design and results of the efficacy and safety study, see Section "7.3.3 Open-label comparative study in pediatric patients with XLH"].

Table 25 shows changes in trough serum burosumab concentration over time in the burosumab group following the multiple subcutaneous doses[15)] of burosumab once every 2 weeks.

Table 25. Changes in trough serum burosumab concentration over time in the burosumab group following multiple subcutaneous doses of burosumab once every 2 weeks

Week 2	Week 4	Week 8	Week 16	Week 24	Week 40	Week 64
4.70 ± 1.23 (n = 26)	7.27 ± 3.19 (n = 28)	10.06 ± 2.87 (n = 29)	10.29 ± 2.42 (n = 29)	10.42 ± 2.97 (n = 29)	11.48 ± 3.88 (n = 29)	10.68 ± 3.36 (n = 29)

Mean ± SD (number of patients); Unit, μg/mL.

Table 26 shows changes in serum phosphorus concentration over time, a parameter of the pharmacodynamic effect of burosumab, in the control group receiving oral phosphate and active vitamin D and in the burosumab group receiving multiple subcutaneous doses of burosumab once every 2 weeks.

Table 26. Changes in serum phosphorus concentration[a)] over time following multiple subcutaneous doses burosumab once every 2 weeks or in multiple administration of oral phosphate plus active vitamin D

	Baseline	Week 2	Week 4	Week 8	Week 12	Week 16	Week 24	Week 32	Week 40
Control	2.30 ± 0.26 (n = 32)	-	2.51 ± 0.32 (n = 32)	2.54 ± 0.35 (n = 32)	-	2.58 ± 0.36 (n = 29)	2.60 ± 0.42 (n = 32)	2.56 ± 0.36 (n = 32)	2.53 ± 0.34 (n = 32)
Burosumab	2.42 ± 0.24 (n = 29)	3.52 ± 0.50 (n = 26)	3.60 ± 0.56 (n = 29)	3.37 ± 0.41 (n = 29)	3.40 ± 0.34 (n = 26)	3.26 ± 0.38 (n = 29)	3.16 ± 0.43 (n = 29)	3.31 ± 0.41 (n = 29)	3.30 ± 0.43 (n = 29)

Mean ± SD (number of patients); Unit, mg/dL; -, Not measured.
a) Values observed under fasting conditions (fasted for ≥4 hours) before burosumab administration

The formation of the anti-burosumab antibody was investigated from baseline before burosumab administration until Week 64. The anti-burosumab antibody was detected at ≥1 evaluation time points in 3 of 29 patients in the burosumab group. All of these 3 patients were positive for the antibody at baseline, and 2 patients were positive after burosumab administration as well. These 3 patients underwent neutralizing antibody testing, with 1 of them found to be positive.

6.2.3 Investigations in patients with TIO or ENS

6.2.3.1 Global phase II study (CTD 5.3.5.2-8, Study KRN23-002 [ongoing since May 2016 (data cut-off May 2018)])

An open-label, uncontrolled study in Japanese and non-Japanese adult patients with TIO or epidermal nevus syndrome (ENS) (target sample size, ≥6 subjects) was conducted to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics following multiple subcutaneous doses of burosumab [for the details of the study design and results of the efficacy and safety study, see Section "7.2.3 Phase II open-label study in patients with TIO or ENS"].

Tables 27 and 28 show changes in pharmacokinetic parameter values and trough serum burosumab concentration over time following multiple subcutaneous doses[16] of burosumab once every 4 weeks.

Table 27. Pharmacokinetic parameters following multiple subcutaneous doses of burosumab once every 4 weeks

	Dose (mg/kg)	Patients	n	C_{max} (μg/mL)	$AUC_{0\text{-}t}$ (μg▪h/mL)	t_{max} (h)
After the first dose	0.3 ± 0.0	Entire population	12	1.49 ± 0.43	730 ± 234	178 [115, 311]
		Japanese	8	1.57 ± 0.49	753 ± 277	168 [115, 309]
		Korean	4	1.34 ± 0.23	683 ± 133	201 [143, 311]
After 20 weeks	0.7 ± 0.4	Entire population	12	7.81 ± 4.31	3620 ± 1860	167 [118, 213]
	0.7 ± 0.4	Japanese	8	8.39 ± 3.80	3950 ± 1620	166 [118, 213]
	0.7 ± 0.5	Korean	4	6.65 ± 5.63	2960 ± 2380	167 [167, 170]

Mean ± SD; t_{max} is expressed in median [range].
C_{max}, maximum serum concentration; $AUC_{0\text{-}4}$, area under serum concentration-time curve from time 0 to Week 4; t_{max}, time to maximum serum concentration

Table 28. Trough serum burosumab concentration following multiple subcutaneous doses of burosumab once every 4 weeks

Patients	Week 4	Week 8	Week 16	Week 20	Week 24	Week 32	Week 36	Week 40	Week 48
Entire population (n = 13)	0.70 ± 0.36[a)]	1.35 ± 0.48	2.39 ± 1.27[a)]	2.96 ± 1.59[a)]	3.77 ± 2.32[a)]	3.48 ± 2.30[a)]	3.73 ± 2.81[a)]	3.72 ± 3.11[b)]	4.16 ± 3.55[a)]
	(0.3 ± 0.0)	(0.5 ± 0.2)	(0.7 ± 0.3)	(0.7 ± 0.4)	(0.7 ± 0.4)	(0.8 ± 0.5)	(0.8 ± 0.6)	(0.9 ± 0.6)	(0.9 ± 0.6)
Japanese (n = 9)	0.78 ± 0.41[c)]	1.36 ± 0.53	2.58 ± 1.45[c)]	3.33 ± 1.61[c)]	4.05 ± 2.29[c)]	3.75 ± 2.08[c)]	3.93 ± 2.60[c)]	3.70 ± 2.76[d)]	3.84 ± 2.77[c)]
	(0.3 ± 0.0)	(0.4 ± 0.2)	(0.7 ± 0.3)	(0.7 ± 0.4)	(0.7 ± 0.4)	(0.8 ± 0.5)	(0.9 ± 0.6)	(0.9 ± 0.6)	(0.9 ± 0.6)
Korean (n = 4)	0.53 ± 0.21	1.33 ± 0.38	2.03 ± 0.89	2.22 ± 1.45	3.21 ± 2.63	2.94 ± 2.97	3.34 ± 3.59	3.76 ± 4.13	4.79 ± 5.25
	(0.3 ± 0.0)	(0.5 ± 0.2)	(0.7 ± 0.3)	(0.6 ± 0.4)	(0.7 ± 0.5)	(0.7 ± 0.5)	(0.8 ± 0.6)	(0.8 ± 0.6)	(0.9 ± 0.5)

Upper row, mean ± SD of serum burosumab concentration (μg/mL)
Lower row, mean ± SD of the dose of burosumab (mg/kg) immediately before each evaluation time point
a) n = 12; b) n = 11; c) n = 8; d) n = 7

Table 29 shows changes in serum phosphorus concentration over time, a parameter of the pharmacodynamic effect of burosumab.

[16] The starting dose was 0.3 mg/kg to be administered subcutaneously once every 4 weeks. The dose up to Week 16 was adjusted within the range from 0.1 to 2 mg/kg, depending on the serum phosphate concentration 2 weeks before the day of administration. The dose from Week 20 was the same as that on Week 16, but could be adjusted if there was any safety concern or if the investigator considered that the dose was unlikely to be effective based on the serum phosphate concentration 4 weeks before.

Table 29. Changes in serum phosphorus concentration[a)] over time following multiple subcutaneous doses of burosumab once every 4 weeks

Patients	Week 0	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
Entire population (n = 13)	1.62 ± 0.49	1.94 ± 0.87[b)]	2.27 ± 0.72	2.44 ± 0.80	2.52 ± 0.68[b)]	2.51 ± 0.58[b)]	2.65 ± 0.62[b)]
	-	(0.3 ± 0.0)	(0.5 ± 0.2)	(0.6 ± 0.2)	(0.7 ± 0.3)	(0.7 ± 0.4)	(0.7 ± 0.4)
Japanese (n = 9)	1.66 ± 0.59	2.04 ± 1.04[c)]	2.22 ± 0.81	2.39 ± 0.84	2.48 ± 0.59[c)]	2.58 ± 0.54[c)]	2.78 ± 0.67[c)]
	-	(0.3 ± 0.0)	(0.4 ± 0.2)	(0.6 ± 0.3)	(0.7 ± 0.3)	(0.7 ± 0.4)	(0.7 ± 0.4)
Korean (n = 4)	1.55 ± 0.13	1.75 ± 0.44	2.38 ± 0.55	2.55 ± 0.83	2.60 ± 0.94	2.38 ± 0.70	2.40 ± 0.48
	-	(0.3 ± 0.0)	(0.5 ± 0.2)	(0.6 ± 0.2)	(0.7 ± 0.3)	(0.6 ± 0.4)	(0.7 ± 0.5)

Patients	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48
Entire population (n = 13)	2.62 ± 0.62[b)]	2.62 ± 0.52[b)]	2.65 ± 0.47[b)]	2.65 ± 0.57[d)]	2.63 ± 0.61[b)]	2.70 ± 0.44[d)]
	(0.7 ± 0.5)	(0.8 ± 0.5)	(0.8 ± 0.6)	(0.8 ± 0.6)	(0.9 ± 0.6)	(0.9 ± 0.6)
Japanese (n = 9)	2.75 ± 0.66[c)]	2.81 ± 0.48[c)]	2.81 ± 0.43[c)]	2.69 ± 0.67[e)]	2.65 ± 0.68[c)]	2.66 ± 0.45[e)]
	(0.8 ± 0.5)	(0.8 ± 0.5)	(0.9 ± 0.6)	(0.9 ± 0.6)	(0.9 ± 0.6)	(0.9 ± 0.6)
Korean (n = 4)	2.35 ± 0.51	2.23 ± 0.40	2.33 ± 0.42	2.58 ± 0.39	2.60 ± 0.54	2.78 ± 0.48
	(0.7 ± 0.5)	(0.7 ± 0.5)	(0.8 ± 0.6)	(0.8 ± 0.6)	(0.9 ± 0.5)	(0.9 ± 0.5)

Upper row, Mean ± SD of serum phosphorus concentration (mg/mL)
Lower row, Mean ± SD of the dose of burosumab (mg/kg) immediately before each evaluation time point; -, Not applicable
a) Values obtained under fasting conditions (fasted for ≥8 hours) before burosumab administration; b) n =12; c) n = 8; d) n = 11; e) n = 7

Before the data cut-off, antibodies were evaluated from baseline through Week 48. At baseline, the anti-burosumab antibody was positive in 1 of 13 patients, but neutralizing antibody was negative. There were no patients with anti-burosumab-positive after the start of burosumab administration.

6.2.3.2 Phase II study in non-Japanese patients (CTD 5.3.5.2-9, Study UX023T-CL201 [ongoing since March 2015 (data cut-off January 2018), Reference data])

An open-label, uncontrolled study in non-Japanese adult patients with TIO or ENS (target sample size, 15 subjects) was conducted to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics following multiple subcutaneous doses of burosumab [for the details of the study design and results of the efficacy and safety study, see Section "7.2.4 Phase II open-label study in non-Japanese patients with TIO or ENS"].

Table 30 shows changes in trough serum burosumab concentration over time following multiple subcutaneous doses[17)] of burosumab once every 4 weeks.

Table 30. Changes in trough serum burosumab concentration[a)] over time following multiple subcutaneous doses of burosumab once every 4 weeks

Week 4	Week 8	Week 16	Week 20	Week 24	Week 32	Week 36	Week 40	Week 48
1.13 ± 0.63	2.01 ± 1.39[a)]	3.17 ± 2.48	3.72 ± 2.52	4.10 ± 3.26	3.35 ± 2.87[b)]	2.52 ± 0.41[c)]	3.14 ± 1.21[c)]	2.82 ± 1.23[d)]
(0.3 ± 0.0)	(0.4 ± 0.2)	(0.7 ± 0.3)	(0.8 ± 0.3)	(0.8 ± 0.4)	(0.8 ± 0.4)	(0.8 ± 0.5)	(0.8 ± 0.5)	(0.8 ± 0.5)

Upper row, Mean ± SD of serum burosumab concentration (μg/mL) (n = 17)
Lower row, Mean ± SD of the dose of burosumab (mg/kg) immediately before each evaluation time point (n = 17)
a) n = 15; b) n = 7; c) n = 4; d) n = 2

Table 31 shows changes in serum phosphorus concentration over time, a parameter of the pharmacodynamic effect of burosumab.

[17)] The starting dose was 0.3 mg/kg to be administered subcutaneously once every 4 weeks. The dose up to Week 16 was adjusted within the range up to 2 mg/kg, depending on the serum phosphate concentration 2 weeks before the day of administration. The dose from Week 20 was the same as that on Week 16, but could be adjusted if there was any safety concern or if the investigator considered that the dose is unlikely to be effective based on the serum phosphate concentration 4 weeks before.

Table 31. Changes in serum phosphorus concentration[a)] over time following multiple subcutaneous doses of burosumab once every 4 weeks

Week 0	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28
1.59 ± 0.43	2.05 ± 0.83[b)]	2.01 ± 0.54	2.28 ± 0.74	2.29 ± 0.54	2.37 ± 0.74[c)]	2.41 ± 0.56	2.60 ± 0.51[c)]
(-)	(0.3 ± 0.0)	(0.4 ± 0.2)	(0.5 ± 0.2)	(0.7 ± 0.3)	(0.8 ± 0.3)	(0.8 ± 0.4)	(0.8 ± 0.4)
Week 32	Week 36	Week 40	Week 44	Week 48	Week 60	Week 72	
2.46 ± 0.58	2.64 ± 0.75[b)]	2.63 ± 0.85[b)]	2.56 ± 0.64[b)]	2.50 ± 0.58[b)]	2.69 ± 0.73[c)]	2.59 ± 0.51[c)]	
(0.8 ± 0.4)	(0.8 ± 0.5)	(0.8 ± 0.5)	(0.8 ± 0.5)	(0.8 ± 0.5)	(0.8 ± 0.5)	(0.8 ± 0.5)	

Upper row, Mean ± SD of serum phosphorus concentration (mg/dL) (n = 17)
Lower row, Mean ± SD of the dose of burosumab (mg/kg) immediately before each evaluation time point (n = 17); -, Not applicable
a) Values observed under fasting conditions (fasted for ≥8 hours) before burosumab administration; b) n =16; c) n = 15

Before the data cut-off, antibody had been evaluated from baseline through Week 48. There were no patients positive for the anti-burosumab antibody.

6.2.4 Pharmacokinetic analysis

6.2.4.1 Population pharmacokinetic analysis in patients with XLH (CTD 5.3.3.5-1)

Using the data of serum burosumab concentration at 2262 measuring points obtained from 115 adult patients with XLH in 5 studies conducted in Japan and foreign countries (foreign phase I study KRN23-US-02, foreign phase I/II studies KRN23-INT-001 and KRN23-INT-002, foreign phase II study UX023-CL203, global phase III study UX023-CL303) and from 65 pediatric patients (1-12 years of age) with XLH in 2 foreign studies (phase II studies UX023-CL201 and UX023-CL205), a population pharmacokinetic analysis was conducted (software used, Phoenix NLME v.7).

The characteristics (median [minimum, maximum]) of patients subjected to the population pharmacokinetic analysis were as follows: In pediatric patients (1-12 years of age) with XLH, age was 8.0 [1.2, 12.0] years, body mass index (BMI) was 18.8 [14.2, 33.1] kg/m^2, height was 115 [77.5, 144] cm, and body weight was 26.4 [9.2, 55.2] kg. In adult patients with XLH, age was 41.6 [19.0, 68.0] years, BMI was 30.2 [19.7, 68.2] kg/m^2, height was 151 [122, 176] cm, and body weight was 70.2 [37.1, 139.6] kg.

A 1-compartment model with first order absorption process was constructed as the basic model. The following parameters were evaluated in a stepwise manner as possible covariates for the estimated parameters in individual patients: Age, age group,[18)] sex, race,[19)] ethnicity,[20)] country studied,[21)] study, anti-burosumab, baseline FGF23 level and its change over time, baseline laboratory values,[22)] and type of *PHEX* gene mutation.[23)] The body weight was included as the fixed effect for V/F and CL/F.

18) Children, adults
19) White, black, Asian, other
20) Hispanic or Latin, non-Hispanic or non-Latin, unknown
21) US, Canada, France, UK, Ireland, Italy, Netherlands, Korea, Japan
22) Albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), creatinine, and creatinine clearance
23) Pathogenic or likely pathogenic mutation, Variants of uncertain significance, Likely benign or no mutation, Not available.

6.R Outline of the review conducted by PMDA

6.R.1 Comparison of pharmacokinetics and pharmacodynamics between Japanese and non-Japanese patients with XLH

The applicant's explanation about the pharmacokinetics and pharmacodynamics in Japanese and non-Japanese patients with XLH:

Table 16 shows the pharmacokinetic parameters following a single subcutaneous dose of burosumab (0.3, 0.6, or 1 mg/kg) in the phase I study (Study KRN23-001) in Japanese and non-Japanese (Korean) adult patients with XLH. The results showed that the pharmacokinetics is similar between Japanese and non-Japanese patients. In contrast, serum phosphorus concentration, a parameter of the pharmacodynamic effect, was higher in Japanese patients in the 0.6 mg/kg group (Table 17). This was possibly due to the higher baseline serum phosphorus concentration in Japanese patients in the 0.6 mg/kg group. Because the change from baseline was similar between the Japanese and the Korean patients, the pharmacodynamic effect is presumed to be similar between these patient groups. Tables 16 and 18 show the pharmacokinetic parameters following a single subcutaneous dose of burosumab in the Japanese subpopulation of Study KRN23-001 and in the foreign phase I study (Study KRN23-US-02). The exposure to burosumab (C_{max} and $AUC_{0-\infty}$) tended to be lower in Japanese patients than in non-Japanese patients. From a pharmacodynamic point of view, no significant difference was observed in changes in serum phosphorus concentration over time between Japanese and non-Japanese patients of the 0.3 or 0.6 mg/kg group, whereas serum phosphorus concentration tended be lower in Japanese patients of the 1 mg/kg group than in non-Japanese patients in the same dose group (Tables 17 and 19). Thus, some of the pharmacokinetic and pharmacodynamic parameters showed lower levels in Japanese patients than in non-Japanese patients, but accurate comparison was practically impossible because of the small number (3 or 4) of patients in each dose group compared and wide inter-individual variability.

Tables 32 and 33 show the comparison of changes in trough serum burosumab and phosphate concentrations over time between Japanese and non-Japanese patients in the global phase III studies (Studies UX023-CL303 and UX023-CL304) subcutaneously administering burosumab (1 mg/kg) to adult patients with XLH once every 4 weeks. The trough serum burosumab concentration at Week 4 after the start of administration did not significantly differ between Japanese and non-Japanese patients. In contrast, the concentration at Week 24 was higher in non-Japanese patients in Study UX023-CL303 but higher in Japanese patients in Study UX023-CL304, failing to show no consistent tendency. Changes in serum phosphorus concentration, a parameter of the pharmacodynamic effect, did not show any significant difference between Japanese and non-Japanese patients in either of the studies.

Table 32. Changes in trough serum burosumab concentration over time following multiple subcutaneous doses of burosumab (1 mg/kg) once every 4 weeks (Studies UX023-CL303 and UX023-CL304)

Study	Patients	Week 4	Week 24
UX023-CL303	Japanese (n)	3.99 ± 1.45 (6)	3.48 ± 1.10 (6)
	Non-Japanese (n)	3.79 ± 1.65 (62)	6.01 ± 3.50 (62)
UX023-CL304	Japanese (n)	4.43 ± 2.09 (4)	6.10 ± 4.39 (4)
	Non-Japanese (n)	3.78 ± 1.46 (10)	4.77 ± 2.26 (10)

Mean ± SD; Unit, μg/mL

Table 33. Changes in serum phosphorus concentration[a)] over time following multiple subcutaneous doses of burosumab (1 mg/kg) once every 4 weeks (Studies UX023-CL303 and UX023-CL304)

Study	Patients	Baseline	Week 4	Week 20	Week 24
UX023-CL303	Japanese (n)	2.03 ± 0.31 (6)	3.18 ± 0.94 (6)	2.58 ± 0.46 (6)	2.63 ± 0.54 (6)
	Non-Japanese (n)	2.03 ± 0.31 (62)	2.97 ± 0.62 (61)	2.72 ± 0.48 (59)	2.52 ± 0.44 (62)
UX023-CL304	Japanese (n)	1.95 ± 0.53 (4)	2.73 ± 0.61 (4)	2.60 ± 0.50 (4)	2.53 ± 0.43 (4)
	Non-Japanese (n)	2.36 ± 0.28 (10)	2.93 ± 0.35 (10)	2.62 ± 0.24 (10)	2.63 ± 0.29 (10)

Mean ± SD; Unit, μg/mL

a) Value measured under fasting conditions (fasted for ≥8 hours) before burosumab administration

Tables 34 and 35 show the comparison of over-time changes in trough serum burosumab concentration and phosphate concentration between Japanese and non-Japanese pediatric patients in the global phase III study (Study UX023-CL301) subcutaneously administering burosumab (0.8 mg/kg) to pediatric patients with XLH once every 2 weeks. Both serum burosumab and phosphate concentrations were lower in Japanese patients than in non-Japanese patients. In contrast, the comparison of over-time changes in serum burosumab and phosphate concentrations in non-Japanese subpopulation in Study UX023-CL301 and in the Japanese phase III study (Study KRN23-003) did not show any significant difference. Because only 2 Japanese patients were investigated in Study UX023-CL301, an accurate analysis was practically impossible on the difference between Japanese and non-Japanese patients in the pharmacokinetics and pharmacodynamics. However, given the results from the Japanese patients in the Japanese phase III study (Study KRN23-003), there is no significant difference either in the pharmacokinetics or pharmacodynamics between Japanese and non-Japanese pediatric patients with XLH.

Table 34. Changes in trough burosumab concentration over time following multiple subcutaneous doses of burosumab (0.8 mg/kg) once every 2 weeks (Studies KRN23-003 and UX023-CL301)

Study	Patients	Week 2	Week 4	Week 8	Week 16	Week 24	Week 40
KRN23-003	Japanese (n = 15)	3.93 ± 0.84	6.38 ± 1.34	8.49 ± 1.92	8.53 ± 2.50	11.05 ± 4.54	11.65 ± 4.61
UX023-CL301	Japanese (n = 2)	3.44, 3.82	4.71, 7.36	7.17, 7.85	7.71, 8.59	6.55, 8.06	7.80, 12.08
	Non-Japanese (n = 27)	4.79 ± 1.24[a)]	7.37 ± 3.28[b)]	10.25 ± 2.89	10.45 ± 2.43	10.65 ± 2.94	11.60 ± 3.96

Mean ± SD (individual values if n = 2); Unit, μg/mL

a) n = 24; b) n = 26

Table 35. Changes in serum phosphorus concentration[a)] over time following multiple subcutaneous doses of burosumab (0.8 mg/kg) once every 2 weeks (Studies KRN23-003 and UX023-CL301)

Study	Patients	Baseline	Week 2	Week 4	Week 8	Week 12	Week 16	Week 24	Week 32	Week 40
KRN23-003	Japanese (n = 15)	2.61 ± 0.32	3.62 ± 0.52	3.73 ± 0.54	3.63 ± 0.43	3.51 ± 0.52	3.48 ± 0.53	3.41 ± 0.48	3.53 ± 0.43	3.51 ± 0.45
UX023-CL301	Japanese (n = 2)	2.0, 2.4	2.6, 2.8	2.6, 3.3	2.5, 3.1	2.7, 3.2	2.5, 2.5	2.5, 2.8	2.5, 2.8	2.2, 3.0
	Non-Japanese (n = 27)	2.44 ± 0.24	3.59 ± 0.45[b)]	3.64 ± 0.55	3.41 ± 0.39	3.44 ± 0.32[b)]	3.31 ± 0.32	3.20 ± 0.41	3.36 ± 0.37	3.36 ± 0.38

Mean ± SD (individual values if n = 2); Unit, mg/dL

a) Study KRN23-003, value measured under fasting conditions (fasted for ≥4 hours); Study UX023-CL301, value measured under fasting conditions (fasted for ≥4 hours) before burosumab administration

b) n = 24

PMDA's view:

Only a limited number of adult and pediatric patients with XLH were investigated in each study, precluding accurate comparison. Nevertheless, the applicant's explanation is acceptable in terms of no clear difference between Japanese and non-Japanese patients in pharmacokinetics and pharmacodynamics of burosumab based on the range of individual values showing no significant difference.

6.R.2 Comparison of pharmacokinetics and pharmacodynamics between Japanese and non-Japanese patients with TIO

The applicant's explanation about the pharmacokinetics and pharmacodynamics in Japanese and non-Japanese patients with TIO:

Tables 27 and 28 show the pharmacokinetic parameters and over-time changes in the serum burosumab concentration following multiple subcutaneous administration of burosumab once every 4 weeks in the phase II study (Study KRN23-002) in Japanese and non-Japanese (Korean) patients with TIO. The results showed that the exposure to burosumab (C_{max} and AUC_{0-t}) was higher in Japanese patients than in non-Japanese patients, but the observed difference was likely caused by the greater inter-individual difference in the exposure (C_{max} and AUC_{0-t}) in Japanese patients. Over-time changes in serum phosphorus concentration, a parameter of the pharmacodynamic effect, were similar between Japanese and Korean patients (Table 29). Tables 36 and 37 show the comparison of over-time changes in trough serum burosumab and phosphate concentrations following multiple subcutaneous administration of burosumab once every 4 weeks between the Japanese subpopulation in Study KRN23-002 and patients in the foreign phase II study (Study UX023T-CL201). No significant difference was observed between Japanese and non-Japanese patients, which suggests that pharmacokinetics and pharmacodynamics are similar between Japanese and non-Japanese patients with TIO.

Table 36. Changes in serum burosumab concentration over time following multiple subcutaneous doses of burosumab once every 4 weeks to Japanese[a)] and non-Japanese[b)] patients with TIO

Patients	Week 4	Week 8	Week 16	Week 20	Week 24	Week 32	Week 36	Week 40	Week 48
Japanese (n = 9)	0.78 ± 0.41[c)]	1.36 ± 0.53	2.58 ± 1.45[c)]	3.33 ± 1.61[c)]	4.05 ± 2.29[c)]	3.75 ± 2.08[c)]	3.93 ± 2.60[c)]	3.70 ± 2.76[d)]	3.84 ± 2.77[c)]
	(0.3 ± 0.0)	(0.4 ± 0.2)	(0.7 ± 0.3)	(0.7 ± 0.4)	(0.7 ± 0.4)	(0.8 ± 0.5)	(0.9 ± 0.6)	(0.9 ± 0.6)	(0.9 ± 0.6)
Non-Japanese (n = 17)	1.13 ± 0.63	2.01 ± 1.39[e)]	3.17 ± 2.48	3.72 ± 2.52	4.10 ± 3.26	3.35 ± 2.87[f)]	2.52 ± 0.41[f)]	3.14 ± 1.21[f)]	2.82 ± 1.23[g)]
	(0.3 ± 0.0)	(0.4 ± 0.2)	(0.7 ± 0.3)	(0.8 ± 0.3)	(0.8 ± 0.4)	(0.8 ± 0.4)	(0.8 ± 0.5)	(0.8 ± 0.5)	(0.8 ± 0.5)

Upper row, Mean ± SD of serum burosumab concentration (μg/mL)
Lower row, Mean ± SD of the dose of burosumab (mg/kg) immediately before each evaluation time point
a) Results obtained from Japanese subpopulation in Study KRN23-002
b) Results obtained from Study UX023T-CL201
c) n = 8; d) n = 7; e) n = 15; f) n = 7; g) n = 4

Table 37. Changes in serum phosphorus concentration[a)] over time following multiple subcutaneous doses of burosumab once every 4 weeks to Japanese[b)] and non-Japanese[c)] patients with TIO

Patients	Week 0	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
Japanese (n = 9)	1.66 ± 0.59	2.04 ± 1.04[d)]	2.22 ± 0.81	2.39 ± 0.84	2.48 ± 0.59[d)]	2.58 ± 0.54[d)]	2.78 ± 0.67[d)]
	(-)	(0.3 ± 0.0)	(0.4 ± 0.2)	(0.6 ± 0.3)	(0.7 ± 0.3)	(0.7 ± 0.4)	(0.7 ± 0.4)
Non-Japanese (n = 17)	1.59 ± 0.43	2.05 ± 0.83[f)]	2.01 ± 0.54	2.28 ± 0.74	2.29 ± 0.54	2.37 ± 0.74[g)]	2.41 ± 0.56
	(-)	(0.3 ± 0.0)	(0.4 ± 0.2)	(0.5 ± 0.2)	(0.7 ± 0.3)	(0.8 ± 0.3)	(0.8 ± 0.4)

Patients	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48
Japanese (n = 9)	2.75 ± 0.66[d)]	2.81 ± 0.48[d)]	2.81 ± 0.43[d)]	2.69 ± 0.67[e)]	2.65 ± 0.68[d)]	2.66 ± 0.45[e)]
	(0.8 ± 0.5)	(0.8 ± 0.5)	(0.9 ± 0.6)	(0.9 ± 0.6)	(0.9 ± 0.6)	(0.9 ± 0.6)
Non-Japanese (n = 17)	2.60 ± 0.51[g)]	2.46 ± 0.58	2.64 ± 0.75[f)]	2.63 ± 0.85[f)]	2.56 ± 0.64[f)]	2.50 ± 0.58[f)]
	(0.8 ± 0.4)	(0.8 ± 0.4)	(0.8 ± 0.5)	(0.8 ± 0.5)	(0.8 ± 0.5)	(0.8 ± 0.5)

Upper row, Mean ± SD of serum phosphorus concentration (mg/dL)
Lower row, Mean ± SD of the dose of burosumab (mg/kg) immediately before each evaluation time point; -, Not applicable
a) Value measured under fasting conditions (fasted for ≥8 hours) before burosumab administration
b) Results obtained from Japanese subpopulation in Study KRN23-002
c) Results obtained from Study UX023T-CL201
d) n = 8; e) n = 7; f) n = 16; g) n = 15

PMDA's view:

The comparison of the pharmacokinetics between the Japanese subpopulation in Study KRN23-002 and the entire population (consisting of the non-Japanese patients) in Study UX023T-CL201 shows a tendency of difference at some evaluation time points, whereas changes in serum phosphorus concentration, a parameter of the pharmacodynamic effect, was not significantly different through Week 48. Although it is difficult to derive an accurate conclusion because of the limited number of patients investigated, PMDA accepts the applicant's explanation that there is no significant difference in the pharmacokinetics or in the pharmacodynamics between Japanese and non-Japanese patients with TIO.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted the data of the studies listed in Table 38 as the main evaluation and reference data on the efficacy and safety.

Table 38. List of main clinical studies on efficacy and safety

Data category	Region	Study	Phase	Study population	No. of patients treated	Outline of dosage regimen	Main endpoint
Evaluation	Foreign	KRN23-INT-001	I/II	Adult patients with XLH	29	Placebo or burosumab was administered subcutaneously once every 4 weeks (with step-wise dose increase, 0.05 → 0.1 → 0.3 → 0.6 mg/kg), 4 doses in total.	Efficacy Safety Pharmacokinetics Pharmacodynamics
	Foreign	KRN23-INT-002	I/II	Adult patients with XLH	23	Multiple subcutaneous administration once every 4 weeks at the same dose as that on Day 84 (the same dose as the fourth dose) in Study KRN23-INT-001	Efficacy Safety Pharmacokinetics Pharmacodynamic
	Foreign	UX023-CL201	II	Pediatric patients with XLH (5-12 years old)	52	Dose titration period: Burosumab was administered subcutaneously for 16 weeks, once every 2 weeks at a dose of 0.1, 0.2, or 0.3 mg/kg (Q2W group), or once every 4 weeks at a dose of 0.2, 0.4, or 0.6 mg/kg (Q4W group). The dose was increased by 0.3 mg/kg as necessary based on the serum phosphorus concentration. Treatment Period: Burosumab was administered for 48 weeks using the same dosage regimen as that in the dose titration period. Treatment Extension Period: Q2W group: The treatment was continued using the same dosage regimen as that in the treatment period. Q4W group: The dose was adjusted based on serum phosphorus concentration. In both groups, burosumab was administered once every 2 weeks for 96 weeks. In all treatment periods, the dose of burosumab could be increased up to 2 mg/kg (maximum dose 90 mg).	Efficacy Safety Pharmacokinetics Pharmacodynamic
	Foreign	UX023-CL205	II	Pediatric patients with XLH (14 years old)	13	Burosumab (0.8 mg/kg) was administered subcutaneously once every 2 weeks for 64 weeks. The dose could be increased to 1.2 mg/kg based on serum phosphorus concentration.	Efficacy Safety Pharmacokinetics Pharmacodynamic
	Global	KRN23-002	II	Adult patients with TIO or ENS	13	Burosumab (0.3 mg/kg) was administered subcutaneously once every 4 weeks. The dose was adjusted within the range from 0.1 to 2 mg/kg, based on serum phosphorus concentration or on the judgment of the investigator, etc.	Efficacy Safety
	Global	UX023-CL303	III	Adult patients with XLH	134	Placebo-controlled period: Placebo or burosumab (1 mg/kg) was administered subcutaneously once every 4 weeks for 24 weeks. Treatment Continuation Period (24 weeks), Treatment Extension Period I (48 weeks), Treatment Extension Period II (53 weeks at the maximum): Burosumab (1 mg/kg) was administered subcutaneously once every 4 weeks. The maximum dose was 90 mg in all periods.	Efficacy Safety
	Global	UX023-CL304	III	Adult patients with XLH	14	Burosumab (1 mg/kg) was administered subcutaneously once every 4 weeks for a maximum of 96 weeks. The maximum dose was 90 mg.	Efficacy Safety
	Global	UX023-CL301	III	Pediatric patients with XLH (1-12 years old)	61	Burosumab (0.8 mg/kg) was administered subcutaneously once every 2 weeks, or the control drugs (oral phosphate and active vitamin D) were administered according to the approved dosage regimen. The dose of burosumab could be increased to 1.2 mg/kg based on the serum phosphorus concentration.	Efficacy Safety

	Japan	KRN23-003	III	Pediatric patients with XLH (1-12 years old)	15	Burosumab (0.8 mg/kg) was administered subcutaneously once every 2 weeks for 86 weeks. The dose could be increased to 1.2 mg/kg based on the serum phosphorus concentration.	Efficacy Safety
Reference	Foreign	UX023T-CL201	II	Adult patients with TIO or ENS	17	Burosumab (0.3 mg/kg) was administered subcutaneously once every 4 weeks for 212 weeks. The dose could be adjusted within the range up to 2 mg/kg based on the serum phosphorus concentration.	Efficacy Safety Pharmacokinetics Pharmacodynamics
	Foreign	UX023-CL203	II	Adult patients with XLH	20	Burosumab was administered subcutaneously for 144 weeks at the same dose as the final dose in Study KRN23-INT-001 or KRN23-INT-002.	Safety Pharmacodynamics Efficacy

In the following are described the main study results.

7.1 Phase I/II studies

7.1.1 Phase I/II dose titration study in non-Japanese adult patients with XLH (5.3.5.2-1, Study KRN23-INT-001 [October 2011-April 2013])

An open-label, dose titration study to investigate the efficacy and safety of burosumab (open-label study) and a placebo-controlled, single-blind study were conducted in non-Japanese[24)] adult patients with XLH (target sample size, 42 subjects; 24 in the open-label study, 18 in bone substudy) to investigate the bone density and bone quality during treatment with burosumab (bone substudy).

The main inclusion criteria in the open-label study were adult patients with XLH with serum FGF23 concentration exceeding 30 pg/mL at the pretreatment test. The inclusion criteria in the bone substudy were, in addition to the above criteria, 18 to 35 years of age and serum alkaline phosphatase (ALP) concentration exceeding 100 U/L at the pretreatment test. Patients were excluded if they took vitamin D, its metabolites, related compounds, or phosphate preparation within 10 days before the visit for the pretreatment test or the baseline test.

The study (open-label study and bone substudy) consisted of the pretreatment test period (maximum 30 days), the dosing period (maximum 110 days), and the follow-up period (maximum 10 days).

Placebo or burosumab was administered subcutaneously once every 4 weeks. The starting dose of burosumab was 0.05 mg/kg. Burosumab was administered subcutaneously for a total of 4 times with a step-wise dose increase (0.05 to 0.1, to 0.3, and to 0.6 mg/kg) according to the serum phosphorus concentration and the safety assessment.

All of the 29 patients receiving the study drug (27 in the open-label study, 1 each[25)] in the placebo group and the burosumab group of the bone substudy) were included in the safety analysis population, and 28 patients (26 in the open-label study; 1 each in the placebo group and the burosumab group of the bone substudy) were included in the efficacy analysis population. One patient was excluded due to unavailability of the result of Day 28 assessment. Study discontinuation occurred in 2 patients in the open-label study. The reason for the discontinuation was adverse events in both of them.

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24) US and Canada

25) The bone substudy was discontinued at the time point when 2 patients were enrolled for the following reasons: (1) The treatment extension study required biopsy from iliac crest, and the patients did not provide consent, and (2) there were only few candidate patients who met the inclusion criteria.

Table 39 shows the percentage of patients classified into each serum phosphorus concentration level after the study drug administration, the primary efficacy endpoint. The serum phosphorus concentration was ≤2.5 mg/dL at baseline in almost all patients receiving burosumab, and peaked on Day 7 after the first dose of burosumab. The percentage of patients showing serum phosphorus concentration of >2.5 mg/mL and ≤3.5 mg/mL on Day 7 after the first dose tended to increase with the increase in the frequency of administration. Serum phosphorus concentration exceeded 4.5 mg/dL in none of the subjects during the treatment period.

Table 39. Percentage of patients classified into each serum phosphorus concentration level after burosumab administration
(Study KRN23-INT-001 [patients receiving burosumab], efficacy analysis population)

Dose number	Dose[a)] (mg/kg)	Days after administration (days after the first dose)	Serum phosphorus concentration (mg/dL)			
			≤2.5	>2.5 and ≤3.5	>3.5 and ≤4.5	>4.5
First	0.05 ± 0.00	Baseline (Day 0)	96.3 (26)	3.7 (1)	0 (0)	0 (0)
		Day 7 after administration (Day 7)	85.2 (23)	14.8 (4)	0 (0)	0 (0)
		Day 26 after administration (Day 26)	96.3 (26)	3.7 (1)	0 (0)	0 (0)
Second	0.10 ± 0.01	Day of administration (Day 28)	96.3 (26)	3.7 (1)	0 (0)	0 (0)
		Day 7 after administration (Day 35)	63.0 (17)	37.0 (10)	0 (0)	0 (0)
		Day 26 after administration (Day 54)	92.6 (25)	7.4 (2)	0 (0)	0 (0)
Third	0.28 ± 0.06	Day of administration (Day 56)	85.2 (23)	7.4 (2)	0 (0)	0 (0)
		Day 7 after administration (Day 63)	25.9 (7)	74.1 (20)	0 (0)	0 (0)
		Day 26 after administration (Day 82)	70.4 (19)	29.6 (8)	0 (0)	0 (0)
Fourth	0.48 ± 0.16	Day of administration (Day 84)	66.7 (18)	22.2 (6)	0 (0)	0 (0)
		Day 7 after administration (Day 91)	11.1 (3)	70.4 (19)	14.8 (4)	0 (0)
		Day 26 after administration (Day 91)	51.9 (14)	44.4 (12)	0 (0)	0 (0)

Percentage of patients (number of patients)
a) Mean ± SD

In the bone substudy, serum phosphorus concentration in 1 patient in the placebo group changed little from the baseline level (1.6 mg/dL), remaining within the range from 1.5 to 2.1 mg/dL.

The incidence of adverse events was 100% (1 of 1) in patient in the placebo group of the bone substudy and 89.3% (25 of 28) in patients receiving burosumab. Table 40 shows the incidence of adverse events reported in ≥3 patients in the burosumab group. Adverse drug reactions were observed in 35.7% (10 of 28) of patients receiving burosumab and not in the placebo group. The adverse drug reaction reported in ≥2 patients receiving burosumab was diarrhoea in 2 patients.

Table 40. Incidences of adverse events reported in ≥3 patients receiving burosumab (Study KRN23-INT-001, safety analysis population)

Event	Open-label study	Bone substudy		All patients receiving burosumab (n = 28)
	Burosumab (n = 27)	Placebo (n = 1)	Burosumab (n = 1)	
All events	88.9 (24)	100 (1)	100 (1)	89.3 (25)
Nasopharyngitis	25.9 (7)	100 (1)	100 (1)	28.6 (8)
Arthralgia	22.2 (6)	0 (0)	100 (1)	25.0 (7)
Diarrhoea	18.5 (5)	0 (0)	0 (0)	17.9 (5)
Restless legs syndrome	18.5 (5)	0 (0)	0 (0)	17.9 (5)
Back pain	14.8 (4)	0 (0)	100 (1)	17.9 (5)
Upper respiratory tract infection	14.8 (4)	0 (0)	0 (0)	14.3 (4)
Headache	11.1 (3)	100 (1)	100 (1)	14.3 (4)
Tooth infection	11.1 (3)	0 (0)	0 (0)	10.7 (3)
Musculoskeletal pain	11.1 (3)	0 (0)	0 (0)	10.7 (3)
Pain in extremity	11.1 (3)	0 (0)	0 (0)	10.7 (3)
Dyspepsia	7.4 (2)	0 (0)	100 (1)	10.7 (3)
Urinary tract infection	7.4 (2)	0 (0)	100 (1)	10.7 (3)
Myalgia	7.4 (2)	0 (0)	100 (1)	10.7 (3)

Incidence % (number of patients), Medical dictionary for regulatory activities (MedDRA) ver. 14.0

There was no death or serious adverse event. An adverse event leading to treatment discontinuation was observed in 1 patient in the burosumab group (injection site urticaria) which was assessed as an adverse drug reaction.

One patient was positive for the anti-burosumab antibody before the study drug administration, but no neutralizing antibody was detected. There were no patients who turned antibody-positive after burosumab administration.

An abnormal vital sign was observed in 1 patient in the burosumab group. The event was assessed as an adverse event (hypertension), which was mild in severity and resolved without any intervening treatment A causal relationship to the study drug was ruled out for the event. Electrocardiogram did not show any clinically significant change.

7.1.2 Treatment continuation study in non-Japanese adult patients with XLH (5.3.5.2-2, Study KRN23-INT-002 [March 2012 to July 2013])

A treatment continuation study was conducted in patients who had completed Study KRN23-INT-001 (target sample size, 35 subjects) in order to investigate the safety and efficacy in the long-term treatment with burosumab.

The starting dose was the same as that used in the last dose (Day 84 of administration) in Study KRN23-INT-001. In patients with baseline serum phosphorus concentration of >3.5 mg/dL in the main study and in patients in whom the maximum serum phosphorus concentration from the start of administration until Day 110 in Study KRN23-INT-001 was ≥4.2 mg/dL, the dose was reduced by 1 level (in the order of 0.6, 0.3, 0.1, and 0.05 mg/kg). Burosumab was administered subcutaneously once every 4 weeks for up to 12 doses, with the dose adjusted as appropriate within the range of 0.05 to 1 mg/kg, based on the serum phosphorus concentration on Day 25 after each dose and safety assessment. Patients who completed the bone substudy of Study KRN23-INT-001 continued to receive placebo or burosumab.

All of the 23 patients receiving the study drug (21 in the open-label study, 1 each in the placebo group and the burosumab group in the bone substudy) were included in the safety and efficacy analysis populations. Study discontinuation occurred in 4 patients. The reasons for the discontinuation were adverse events in 2 patients (burosumab group in the open-label study) and the sponsor's decision (discontinuation of bone substudy) in 2 patients (1 each in the placebo group and the burosumab group in the bone substudy).

Table 41 shows the percentage of patients classified into each level of serum phosphorus concentration after the study drug administration, the primary efficacy endpoint.

Table 41. Percentage of patients in each serum phosphorus concentration level after burosumab administration (Study KRN23-INT-002 [patients receiving burosumab], efficacy analysis population)

Dose number	Dose[a)] (mg/kg)	Days after administration (days after the first dose)	Serum phosphorus concentration (mg/dL)			
			≤2.5	>2.5 and ≤3.5	>3.5 and ≤4.5	>4.5
First	0.54 ± 0.20	Day of administration (Day 0)	100 (21)	0 (0)	0 (0)	0 (0)
		Day 7 after administration (Day 7)	18.2 (4)	77.3 (17)	4.5 (1)	0 (0)
		Day 14 after administration (Day 14)	18.2 (4)	81.8 (18)	0 (0)	0 (0)
		Day 25 after administration (Day 25)	68.2 (15)	31.8 (7)	0 (0)	0 (0)
12th	0.83 ± 0.28	Day of administration (Day 308)	73.7 (14)	26.3 (5)	0 (0)	0 (0)
		Day 7 after administration (Day 315)	42.1 (8)	47.4 (9)	10.5 (2)	0 (0)
		Day 14 after administration (Day 322)	47.4 (9)	52.6 (10)	0 (0)	0 (0)
		Day 25 after administration (Day 333)	63.2 (12)	36.8 (7)	0 (0)	0 (0)

Percentage of patients (number of patients)
a) Mean ± SD

In the bone substudy, serum phosphorus concentration in 1 patient in the placebo group was 1.6 mg/dL and remained almost unchanged within the range from 1.7 to 2.0 mg/dL until the end of the study (1.8 mg/dL).

The incidence of adverse events was 100% (23 of 23) in patients receiving burosumab and the placebo group combined. Table 42 shows the incidence of adverse events reported in ≥3 patients receiving burosumab. Adverse drug reactions were observed in 63.6% (14 of 22) of patients receiving burosumab and none in the placebo group. Adverse drug reactions reported in ≥2 patients receiving burosumab were injection site reaction in 5 patients (22.7%), arthralgia in 3 patients (13.6%), injection site pain and restless legs syndrome in 2 patients each (9.1%).

Table 42. Adverse events reported in ≥3 patients receiving burosumab (Study KRN23-INT-002, safety analysis population)

Event	Open-label study	Bone substudy		All patients receiving burosumab (n = 22)
	Burosumab (n = 21)	Placebo (n = 1)	Burosumab (n = 1)	
All events	100 (21)	100 (1)	100 (1)	100 (22)
Sinusitis	28.6 (6)	0 (0)	0 (0)	27.3 (6)
Arthralgia	28.6 (6)	0 (0)	0 (0)	27.3 (6)
Injection site reaction	23.8 (5)	0 (0)	0 (0)	22.7 (5)
Back pain	23.8 (5)	0 (0)	0 (0)	22.7 (5)
Abdominal discomfort	19.0 (4)	0 (0)	0 (0)	18.2 (4)
Pain in extremity	19.0 (4)	0 (0)	0 (0)	18.2 (4)
Dizziness	19.0 (4)	0 (0)	0 (0)	18.2 (4)
Vertigo	14.3 (3)	0 (0)	0 (0)	13.6 (3)
Abdominal pain upper	14.3 (3)	0 (0)	0 (0)	13.6 (3)
Diarrhoea	14.3 (3)	0 (0)	0 (0)	13.6 (3)
Fatigue	14.3 (3)	0 (0)	0 (0)	13.6 (3)
Tooth fracture	14.3 (3)	0 (0)	0 (0)	13.6 (3)
Gastroenteritis viral	14.3 (3)	0 (0)	0 (0)	13.6 (3)
Restless legs syndrome	14.3 (3)	0 (0)	0 (0)	13.6 (3)
Nasopharyngitis	9.5 (2)	100 (1)	100 (1)	13.6 (3)
Headache	9.5 (2)	0 (0)	100 (1)	13.6 (3)

Incidence % (number of patients), MedDRA ver. 14.0

No death occurred. Serious adverse events were observed in 3 patients receiving burosumab (breast cancer, hypertensive crisis, and cervical spinal stenosis in 1 patient each), but a causal relationship to the study drug was ruled out for all events. Adverse events leading to treatment discontinuation were observed in 2 patients receiving burosumab (nephrolithiasis and restless legs syndrome in 1 patient each), and both of the events were assessed as adverse drug reactions.

There were no patients who turned positive for the anti-burosumab antibody during the study period.

Vital signs and electrocardiogram did not show any clinically significant change.

7.2 Phase II studies

7.2.1 Phase II open-label, dose-finding study in non-Japanese pediatric patients with XLH (5.3.5.2-5, Study UX023-CL201 [ongoing since July 2014 (data cut-off December 2016)])

An open-label, dose-finding study in non-Japanese[26)] pediatric patients with XLH (target sample size; 30 subjects at the beginning of the study, 50 subjects after the revision of the study protocol) was conducted to investigate the efficacy, safety, and pharmacodynamics of burosumab.

The main inclusion criteria were patients aged 5 to 12 years with *PHEX* gene mutation (or the mutation is observed in a consanguineous family) or with serum FGF23 concentration of ≥30 pg/mL, who met both of the following criteria: (a) serum phosphorus concentration of ≤2.8 mg/dL at the second pretreatment test (before the start of burosumab administration)[27)]; and (b) progressive bone disorder including rachitic findings in wrists and knees, or radiographic image showing curved femur or shin

[26)] US, UK, France, and Netherlands
[27)] Measured after fasting for ≥4 hours.

bone (or rickets severity score [RSS][28)] of the knee of ≥1.5 by the central assessment in the extension study). Patients were excluded if they took vitamin D, its metabolites, or related drugs within 14 days before the second pretreatment test and patients who took oral phosphate within 7 days.

The study consisted of a screening period (2-4 weeks), a study drug treatment period (dose titration period, 16 weeks; dosing period, 48 weeks), and a treatment extension period (96 weeks at the maximum).

During the study drug treatment period, burosumab was administered subcutaneously. In the burosumab Q2W group, the starting dose was 0.1 mg/kg in Cohort 1, 0.2 mg/kg in Cohort 2, and 0.3 mg/kg in Cohort 3, once every 2 weeks. In the burosumab Q4W group, the starting dose was 0.2 mg/kg in Cohort 1, 0.4 mg/kg in Cohort 2, and 0.6 mg/kg in Cohort 3, once every 4 weeks. The dose was adjusted once every 4 weeks. Depending on the serum phosphorus concentration at Week 2 after administration, the dose could be increased by 0.3 mg/kg (Q2W group) or 0.4 mg/kg (Q4W group), up to 2 mg/kg. At and after Week 18, the dose was increased to 15 mg if the previous dose was <15 mg and, if the previous dose was ≥15 mg, the dose was rounded to the nearest 10 mg, with the maximum dose being 90 mg. Burosumab was injected into the abdomen, upper arm, or thigh, and the injection site was changed at every injection. During the treatment extension period, all patients received the injection once every 2 weeks. For patients in the burosumab Q2W group, the dose of burosumab was adjusted within the target range during the study drug administration. For patients in the burosumab Q4W group, the dose of burosumab was adjusted to achieve serum phosphorus concentration within the target range.

All of the 52 patients receiving the study drug (26 each in the burosumab Q2W and Q4W groups; 5 in Cohort 1, 5 in Cohort 2, and 16 in Cohort 3 in each treatment group) were included in the safety analysis population, intent-to-treat (ITT) population, and PK/PD analysis population. All patients completed the study drug treatment period. At the data cut-off (when all patients completed the 67-week treatment with the study drug), all patients were continuing the administration up to Week 64 after the start of administration.

Table 43 shows the results of total RSS score, the primary efficacy endpoint, and main secondary efficacy endpoints.

[28)] Radiographic images of wrist and knee joints of all patients were taken over time before and after the start of administration. The images were viewed and evaluated by a single independent expert radiologist blinded to the evaluation time point and all other patient information. The highest score was 4 for wrist joints and 6 for knee joints and, with 10 points assigned to severe rickets and 0 point to the rickets-free conditions. The RSS score was developed to assess the severity of rickets in wrist and knee joints based on the degree of metaphyseal fraying and cupping, and the proportion of the growth plate affected (*J Trop Pediatr.* 2000;46:132-9).

Table 43. Results of the primary endpoint and main secondary endpoints (Study UX023-CL201 [study drug treatment period (Week 64)], ITT population)

Endpoint		Evaluation time point	Burosumab Q2W (n = 26)	Burosumab Q4W (n = 26)
Total RSS		Baseline[a)]	1.92 ± 1.17	1.67 ± 1.00
		Week 40[b)]	0.75 ± 0.55	1.06 ± 0.54
			−1.06 ± 0.11	−0.73 ± 0.10
		Week 64[b)]	0.81 ± 0.60	0.94 ± 0.52
			−1.00 ± 0.11	−0.84 ± 0.10
Wrist RSS		Baseline[a)]	0.71 ± 0.62	0.48 ± 0.52
		Week 40[b)]	0.17 ± 0.24	0.40 ± 0.32
			−0.44 ± 0.05	−0.18 ± 0.06
		Week 64[b)]	0.31 ± 0.32	0.35 ± 0.28
			−0.30 ± 0.06	−0.24 ± 0.05
Knee RSS		Baseline[a)]	1.21 ± 0.68	1.19 ± 0.60
		Week 40[b)]	0.58 ± 0.50	0.65 ± 0.34
			−0.63 ± 0.10	−0.55 ± 0.07
		Week 64[b)]	0.50 ± 0.47	0.60 ± 0.38
			−0.70 ± 0.09	−0.61 ± 0.07
Height Z-score		Baseline[a)]	−1.72 ± 1.03	−2.05 ± 0.96
		Week 64[b)]	−1.54 ± 1.13	−1.92 ± 0.84
			0.19 ± 0.05	0.12 ± 0.06
RGI-C score[29)]	Global score	Week 40[c)]	+1.66 ± 0.09	+1.47 ± 0.14
		Week 64[c)]	+1.56 ± 0.11	+1.58 ± 0.11
	Knee score	Week 40[c)]	+1.60 ± 0.11	+1.34 ± 0.15
		Week 64[c)]	+1.57 ± 0.10	+1.53 ± 0.10
	Wrist score	Week 40[c)]	+1.63 ± 0.15	+1.46 ± 0.13
		Week 64[c)]	+1.65 ± 0.15	+1.55 ± 0.12
Growth rate (cm/year)		Baseline[a)]	5.45 ± 1.17[e)]	5.24 ± 1.40[f)]
		Week 64[d)]	6.14 ± 1.47[e)]	5.67 ± 1.22[f)]
			+0.73 ± 1.40[e)]	+0.37 ± 2.16[f)]
6MWT (m)		Baseline[a)]	479.92 ± 84.80	486.34 ± 108.55
		Week 64[b)]	533.85 ± 58.70	525.85 ± 89.53
			+52.67 ± 8.82	+40.59 ± 9.57
Serum phosphorus concentration (mg/dL)		Baseline[a)]	2.38 ± 0.41	2.28 ± 0.30
		Week 40[d)]	3.30 ± 0.40	2.85 ± 0.31
			0.92 ± 0.48	0.57 ± 0.27
		Week 64[d)]	3.35 ± 0.45[f)]	2.96 ± 0.32[g)]
			0.99 ± 0.50[f)]	0.69 ± 0.37[g)]

a) Mean ± SD
b) Upper row, Mean ± SD; Lower row, Least squares mean ± SE of change from baseline (calculated by generalized estimating equation using the data obtained from measurements over time)
c) Least squares mean ± SE (calculated by generalized estimating equation using the data obtained from measurements over time)
d) Upper row, Mean ± SD; Lower row, Mean ± SD of change from baseline
e) n = 25
f) n = 24
g) n = 23

Figure 1 shows changes in serum phosphorus concentration over time. In the Q2W group, phosphate concentration persistently exceeded the lower limit of normal of 3.2 mg/dL whereas, in the Q4W group, the trough concentration was below the lower limit of normal.

[29)] Radiographic global impression of change (RGI-C) score is used to evaluate change in the severity of rickets according to the 7-point rating system, from −3 points (rickets or curvature has worsened or aggravated very much) to +3 points (the symptoms have improved very much; rickets have been cured completely or almost completely, or the curvature has improved significantly). The evaluation was conducted under blinded conditions by 3 expert pediatric radiologists independent from the study according to the radiographic imaging of wrists, knees, and long lower limb. The RGI-C global score is a comprehensive score based on changes in radiographic images of knees and wrists.

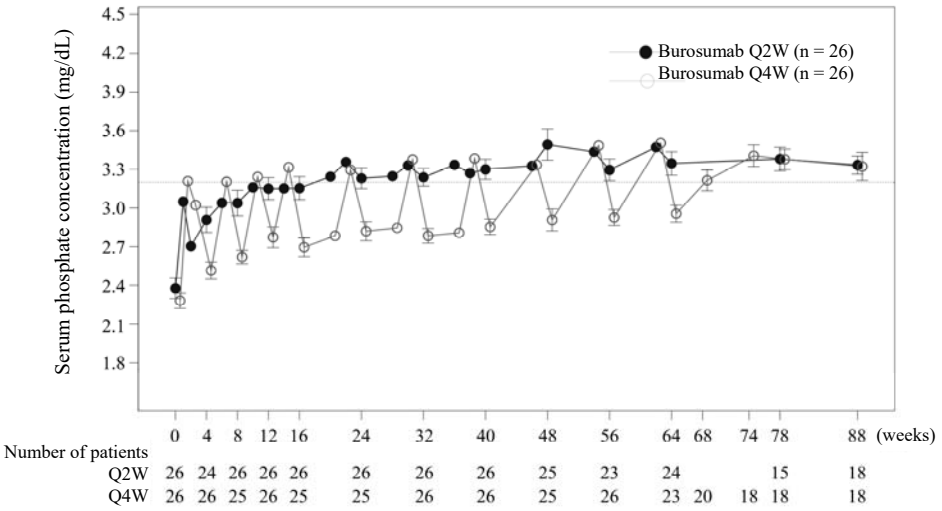

Figure 1. Changes in serum phosphorus concentration over time up to Week 88 (Study UX023-CL201; PK/PD analysis population, mean ± SE)

The incidence of adverse events was 100% (26 of 26) in patients in both burosumab Q2W and Q4W groups. The incidence of adverse drug reactions was 65.4% (17 of 26) in patients in the burosumab Q2W group and 73.1% (19 of 26) in those in the burosumab Q4W group. Table 44 shows the incidences of adverse events reported in ≥20% of patients in either group.

Table 44. Adverse events reported in ≥20% of patients in either group (Study UX023-CL201, safety analysis population)

Event	Burosumab Q2W (n = 26)	Burosumab Q4W (n = 26)
All events	100 (26)	100 (26)
Headache	69.2 (18)	61.5 (16)
Cough	65.4 (17)	42.3 (11)
Injection site erythema	46.2 (12)	30.8 (8)
Nasopharyngitis	42.3 (11)	53.8 (14)
Pain in extremity	38.5 (10)	53.8 (14)
Vomiting	38.5 (10)	46.2 (12)
Upper respiratory tract infection	38.5 (10)	42.3 (11)
Injection site reaction	38.5 (10)	42.3 (11)
Pyrexia	34.6 (9)	38.5 (10)
Arthralgia	30.8 (8)	46.2 (12)
Oropharyngeal pain	30.8 (8)	34.6 (9)
Nasal congestion	26.9 (7)	26.9 (7)
Rash	26.9 (7)	23.1 (6)
Diarrhoea	19.2 (5)	30.8 (8)
Seasonal allergy	19.2 (5)	30.8 (8)
Toothache	19.2 (5)	23.1 (6)
Abdominal pain upper	15.4 (4)	30.8 (8)
Rhinorrhoea	15.4 (4)	30.8 (8)
Myalgia	11.5 (3)	23.1 (6)

Incidence % (number of patients), MedDRA ver. 18.1

No death occurred. Serious adverse events were observed in 1 patient in the burosumab Q4W group (pyrexia and myalgia), and both adverse events were assessed as adverse drug reactions. There were no adverse events leading to treatment discontinuation.

The anti-burosumab antibody was positive at baseline in 1 patient in the burosumab Q2W group and in 3 patients in the burosumab Q4W group, but none were positive for neutralizing antibody. There were no patients who turned antibody-positive after the start of burosumab administration.

Vital signs and electrocardiogram did not show any clinically significant changes.

7.2.2 Phase II open-label study in non-Japanese pediatric patients with XLH (5.3.5.2-6, Study UX023-CL205 [ongoing since May 2016 (data cut-off April 2017)])

An open-label, uncontrolled study in non-Japanese[30)] pediatric patients with XLH (target sample size, 10 subjects) was conducted to investigate the safety and efficacy of burosumab.

The main inclusion criteria were patients aged 1 to 4 years with XLH who met all of the following: (1) have a*PHEX* gene mutation or mutation with unknown clinical significance was detected in a parent or a consanguineous family member with X-linked inheritance; (2) serum phosphorus concentration at pretreatment test[27)] was <3.0 mg/dL; and (3) rickets was confirmed by radiographic imaging. Patients who could not discontinue oral phosphate, vitamin D, its metabolites, or related drugs during the screening period or the study period were excluded.

The study consisted of a screening period (6 weeks at the maximum) and a study drug treatment period (64 weeks).

The starting dose was 0.8 mg/kg administered subcutaneously once every 2 weeks. If the patient met the dose adjustment criteria (i.e., the patient met all of the following criteria: (1) serum phosphorus concentration was below the normal range in 2 consecutive measurements; (2) increase in serum phosphorus concentration from baseline was <0.5 mg/dL; and (3) burosumab was appropriately administered as specified), the dose could be increased to 1.2 mg/kg once every 2 weeks. Burosumab was injected into the abdomen, upper arm, or thigh, and the injection site was changed at every dose.

All of the 13 patients receiving the study drug were included in the safety and efficacy analysis population. At the data cut-off (when all patients completed the 40-week treatment with the study drug), all patients continued the treatment through 40 weeks after the start of administration.

Table 45 shows the changes in serum phosphorus concentration from baseline, the primary efficacy endpoint, and main secondary efficacy endpoints.

30) US

Table 45. Results of the primary endpoint and main secondary endpoints (Study UX023-CL205 [study drug treatment period (Week 40)]; FAS)

Endpoint		Evaluation time point	Burosumab (n = 13)
Serum phosphorus concentration (mg/dL)		Baseline[a)]	2.51 ± 0.28
		Week 40[b)]	3.47 ± 0.49
			0.96 ± 0.44
Total RSS		Baseline[a)]	2.92 ± 1.37
		Week 40[b)]	1.19 ± 0.52
			−1.73 ± 1.20
Supine or standing height Z-score		Baseline[a)]	−1.38 ± 1.19
		Week 40[b)]	−1.65 ± 1.12
			−0.28 ± 0.66
RGI-C score	Global score	Week 40[c)]	+2.33 ± 0.08
	Knee score	Week 40[c)]	+2.21 ± 0.15
	Wrist score	Week 40[c)]	+2.26 ± 0.11
	Long leg score	Week 40[c)]	+1.26 ± 0.14
Serum ALP concentration (U/L)		Baseline[a)]	548.5 ± 193.8
		Week 40[b)]	335.4 ± 87.6
			−213.1 ± 132.5

a) Mean ± SD
b) Upper row, Mean ± SD; Lower row, Mean ± SD of change from baseline
c) Least squares mean ± SE (calculated using a covariance analysis model)

Adverse events occurred in 100% (13 of 13) of patients. Table 46 shows adverse events reported in ≥3 patients. Adverse drug reactions were observed in 38.5% (5 of 13) of patients, which were arthralgia/bone pain/nausea/pain in extremity, injection site erythema/contusion, injection site pruritus, injection site reaction, and blood parathyroid hormone increased in 1 patient each.

Table 46. Adverse events reported in ≥3 patients (Study UX023-CL205, safety analysis population)

Event	Burosumab (n = 13)
All events	100 (13)
Cough	76.9 (10)
Pyrexia	61.5 (8)
Upper respiratory tract infection	53.8 (7)
Vomiting	46.2 (6)
Rhinorrhoea	38.5 (5)
Diarrhoea	30.8 (4)
Pharyngitis streptococcal	30.8 (4)
Tooth abscess	23.1 (3)
Nasal congestion	23.1 (3)
Oral pain	23.1 (3)
Skin abrasion	23.1 (3)
Arthralgia	23.1 (3)
Pain in extremity	23.1 (3)

Incidence % (number of patients), MedDRA ver. 18.1

No death occurred. A serious adverse event was observed in 1 patient (tooth abscess), but its causal relationship to the study drug was ruled out. There was no adverse event leading to treatment discontinuation.

There were no patients who turned positive for the anti-burosumab antibody during the study period.

Vital signs and electrocardiogram did not show any clinically significant changes.

7.2.3 Phase II open-label study in patients with TIO or ENS (5.3.5.2-8, Study KRN23-002 [ongoing since May 2016 (data cut-off May 2018)])

An open-label, uncontrolled study in Japanese and non-Japanese[31)] patients with TIO or ENS (target sample size, ≥6 subjects) was conducted to investigate the efficacy and safety of burosumab [for the results of the pharmacokinetics and pharmacodynamics, see Section "6.2.3.1 Global phase II study"].

The main inclusion criteria were adult patients with a diagnosis of TIO or ENS based on excess FGF23 who were ineligible for surgical resection of tumor/lesion and had serum phosphorus concentration of <2.5 mg/dL and serum FGF23 concentration of ≥100 pg/mL at the pretreatment test. Patients were excluded if they took vitamin D, its metabolites, or related drugs, or oral phosphate for the treatment of TIO or ENS within 14 days before the pretreatment test.

The study consisted of a screening period (up to 56 days) and a study drug treatment period (up to 144 weeks).

Burosumab was administered subcutaneously once every 4 weeks to the abdomen, the upper arm, or the thigh. The starting dose was 0.3 mg/kg, and the dose until Week 16 was adjusted within the range from 0.1 to 2 mg/kg according to the dose adjustment criteria shown in Table 47, based on the serum phosphorus concentration measured 2 weeks before burosumab administration (Weeks 4, 8, 12 and 16). The dose from Week 20 was the same as that at Week 16 but could be adjusted if there was a safety concern or when the investigator considered that the dose was unlikely to be effective based on the serum phosphorus concentration 4 weeks before. When necessary, the dose was increased by 0.2 mg/kg, except for the first dose increase from 0.3 mg/kg, which was to be increased to 0.6 mg/kg for next dose. From Week 92 onward, the dose (in mg) was calculated from the most recent body weight and dose of burosumab, which was rounded to the nearest 10 mg. In Japanese patients, self-injection at home or at the clinical institution was allowed from Week 48.

Table 47. Criteria for dose adjustment

Serum phosphorus concentration 2 weeks before burosumab administration (mg/dL)	Dose adjustment
≤2.5 mg/dL	Increase by 0.2 mg/kg[a)]
>2.5 mg/dL and ≤4.0 mg/dL	No change
>4.0 mg/dL and ≤4.5 mg/dL	Decrease by 0.2 mg/kg
>4.5 mg/dL	Treatment interruption

a) The dose after the first increment from 0.3 mg/kg was 0.6 mg/kg.

All of the 13 patients who received the study drug were included in the safety and efficacy analysis population. At the data cut-off (data through Week 88 in all patients), 12 patients completed the evaluation at Week 88, while 1 patient discontinued the study because of the aggravated primary disease.

Figure 2 shows serum phosphorus concentration (mean ± SD), the primary efficacy endpoint, and Table 48 shows the results of the primary endpoint and the main secondary endpoints. After the first dose of 0.3 mg/kg, serum phosphorus concentration increased from baseline and peaked at Week 2. The subsequent mean serum phosphorus concentrations at Week 48, 72, and 88 remained above the lower limit of normal (2.5 mg/dL). The mean serum phosphorus at the midpoint of each treatment cycle

31) Korea

through Week 24 exceeded the lower limit of normal (2.5 mg/dL) in 69.2% (9 of 13) of patients, and the mean serum phosphorus concentration at the end of each treatment cycle through Week 48 exceeded the lower limit of normal (2.5 mg/dL) in 46.2% (6 of 13) of patients.

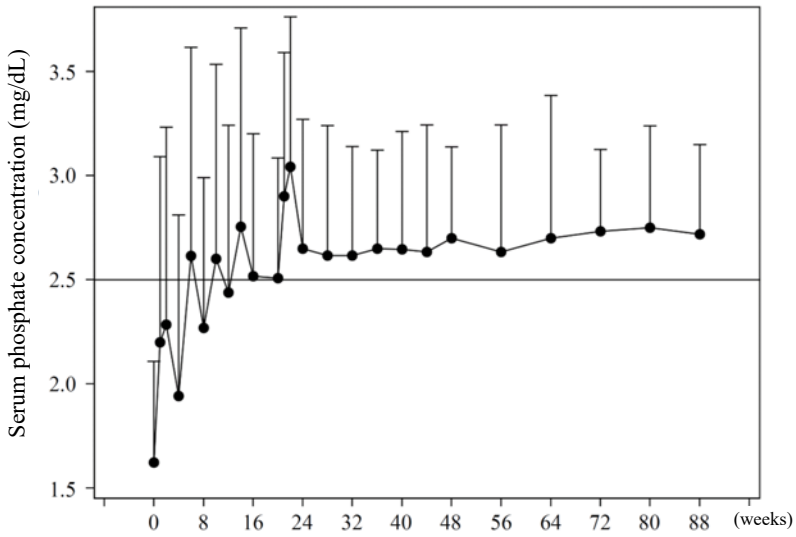

Figure 2. Changes in serum phosphorus concentration over time through Week 88 (Study KRN23-002; efficacy analysis population, mean + SD)

Table 48. Results of the primary endpoint and the main secondary endpoints (Study KRN23-002 [study drug treatment period], FAS)

Analyte	Burosumab (n = 13)			
	Baseline	Week 24	Week 48	Week 72
Serum phosphorus concentration (mg/dL)	1.62 ± 0.49	2.65 ± 0.62[a)]	2.70 ± 0.44[b)]	2.73 ± 0.39[a)]
Serum 1,25$(OH)_2$D concentration (pg/mL)	22.58 ± 11.87	45.29 ± 12.83[a)]	49.29 ± 10.89[b)]	41.34 ± 8.53[a)]
TmP/GFR(mg/dL)	1.148 ± 0.426[a)]	2.304 ± 0.712[a)]	2.303 ± 0.484[b)]	2.291 ± 0.496[a)]
Serum ALP concentration (U/L)	424.7 ± 184.8	454.0 ± 249.2[a)]	374.5 ± 152.2[b)]	365.1 ± 142.8[a)]
Worst BPI score	4.4 ± 2.6	3.0 ± 2.7[a)]	2.9 ± 2.9[a)]	2.9 ± 2.7[a)]
STS	9.9 ± 4.5[a)]	13.3 ± 4.0[b)]	14.1 ± 4.0[b)]	-
6MWT (m)	295.8 ± 96.0	329.2 ± 115.0[a)]	353.7 ± 115.8[a)]	-

Mean ± SD; -, Not evaluated
a) n = 12; b), n = 11

The incidence of adverse events was 92.3% (12 of 13) of patients. Table 49 shows the incidence of adverse events reported in ≥2 patients. Adverse drug reactions were observed in 38.5% (5 of 13) of patients, which were glaucoma/insomnia/vertigo, arthralgia/cataract/dry eye/fatigue/toothache, abdominal pain/hypoaesthesia/myalgia, rash, and injection site hypersensitivity in 1 patient each.

Table 49. Adverse events reported in ≥2 patients (Study KRN23-002, safety analysis population)

Event	Burosumab (n = 13)
All events	92.3 (12)
Nasopharyngitis	61.5 (8)
Fatigue	23.1 (3)
Contusion	23.1 (3)
Constipation	15.4 (2)
Nausea	15.4 (2)
Cystitis	15.4 (2)
Herpes zoster	15.4 (2)
Septic shock	15.4 (2)
Tooth fracture	15.4 (2)
Arthralgia	15.4 (2)
Myalgia	15.4 (2)
Headache	15.4 (2)
Eczema	15.4 (2)
Pruritus	15.4 (2)
Rash	15.4 (2)

Incidence % (number of patients), MedDRA ver. 21.0

No death occurred. Serious adverse events were observed in 3 patients, which were septic shock/gastroenteritis, septic shock, and herpes zoster in 1 patient each. A causal relationship to the study drug was ruled out for all events. There were no adverse events leading to treatment discontinuation.

Baseline anti-burosumab antibody was positive in 1 patient, but neutralizing antibody was negative. There were no patients who turned anti-burosumab antibody-positive after the start of burosumab administration.

Vital signs and electrocardiogram did not show any clinically significant changes.

7.2.4 Phase II open-label study in non-Japanese patients with TIO or ENS (5.3.5.2-9, Study UX023T-CL201 [ongoing since March 2015 (data cut-off January 2018)], Reference data)

An open-label, uncontrolled study in non-Japanese[32)] patients with TIO or ENS (target sample size, 15 subjects) was conducted to investigate the efficacy and safety of burosumab [for results of pharmacokinetics and pharmacodynamics, see Section "6.2.3.2 Phase II study in non-Japanese patients"].

The main inclusion criteria were adult patients diagnosed to have TIO or ENS based on excess FGF23 who were ineligible for surgical resection of tumor/lesion and showed serum phosphorus concentration of <2.5 mg/dL and serum FGF23 concentration of ≥100 pg/mL at the pretreatment test. Patients were excluded if they took vitamin D, its metabolites, related drugs, or oral phosphate for the treatment of TIO or ENS within 2 weeks before the pretreatment test or during the study.

The study consisted of a screening period (4 weeks), a study drug treatment period (48 weeks), a treatment extension period (168 weeks), and a follow-up period (8 weeks).

32) US

Burosumab was administered subcutaneously once every 4 weeks to the abdomen, the upper arm or the thigh. The starting dose was 0.3 mg/kg, and the dose was adjusted through Week 16 according to the dose adjustment criteria shown in Table 50 based on the serum phosphorus concentration measured 2 weeks before burosumab administration (Weeks 4, 8, 12 and 16). From Week 20 onward, treatment was continued with the dose at Week 16 but could be adjusted if there was a safety concern or if considered appropriate based on the serum phosphorus concentration immediately before administration. The dose was increased by 0.2 mg/kg as necessary. However, the dose after the first increment from 0.3 mg/kg was 0.6 mg/kg. The maximum dose was 2 mg/kg. The injection volume was <1.5 mL per site. If the injection volume exceeded 1.5 mL, the study drug was injected to multiple sites.

Table 50. Criteria for dose adjustment

Serum phosphorus concentration 2 weeks before burosumab administration (mg/dL)	Dose adjustment[a)]
≤2.5 mg/dL	Increased by 0.2 mg/kg[b)]
>2.5 mg/dL and ≤4.0 mg/dL	No change
>4.0 mg/dL and ≤4.5 mg/dL	Decrease by 0.2 mg/kg
>4.5 mg/dL	Treatment interruption

a) If serum phosphorus concentration did not increase by ≥0.2 mg/dL after 2 consecutive increments, no further dose increase was to be performed.
b) The only dose after the first increment from 0.3 mg/kg was to be 0.6 mg/kg.

All of the 17 patients receiving the study drug (14 with TIO, 1 with ENS, 2 with XLH, 2[33)]) were included in full analysis set (FAS), and 13 patients of those in FAS who had bone biopsy data at baseline and follow-up were included in the biopsy analysis set. At the data cut-off (when all patients completed the 72-week treatment with the study drug), 3 patients discontinued the study (investigator's decision, death, no increase in serum phosphorus concentration).

A primary efficacy endpoint was the percentage of patients [95% confidence interval (CI)] achieving mean serum phosphorus above the lower limit of normal (2.5 mg/dL) at the midpoint (Weeks 2, 6, 10, 14, 18, and 22) between baseline and Week 24 of each treatment cycle. The value was 52.9% (9 of 17 of patients [30.96%, 73.83%]). Figure 3 shows over-time changes in serum phosphorus concentration in each treatment cycle.

33) The patient was enrolled in the study as a patient with TIO. However, the patient was later found to have no record of tumors and have a history of childhood rickets. The patient underwent a test for *PHEX* gene and was found to have *PHEX* gene mutation, from which the patient had a diagnosis of XLH.

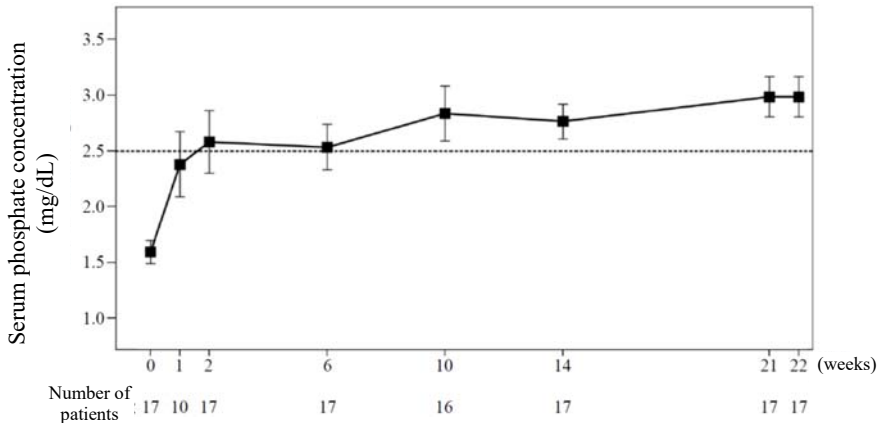

Figure 3. Over-time change in serum phosphorus concentration through Week 22 (Study UX023T-CL201; FAS, mean ± SE)

Histomorphological parameters of bone biopsy samples were another primary efficacy endpoint. The osteoid volume/bone volume (OV/BV) ratio, osteoid thickness (O.Th), and mineralization lag time (MLt) tended to decrease from baseline, while the osteoid surface/bone surface (OS/BS) ratio did not show any significant change (Table 51).

The main secondary endpoint was the percentage of patients with the mean of serum phosphorus concentration higher than the lower limit of normal (2.5 mg/dL) at the end of each treatment cycle during the 24-week treatment period from baseline. The value was 23.5% (4 of 17 of patients).

Table 51. Results with histomorphological parameters evaluation using bone biopsy samples (Study UX023T-CL201 [Week 48], biopsy analysis set)

Evaluation item	Burosumab (n = 13)		
	Baseline	Week 48	Change up to Week 48[a)]
OV/BV (%)	17.02 ± 18.19	12.19 ± 14.21	−4.82 [−10.27, 0.62]
OS/BS (%)	57.62 ± 30.43	58.77 ± 25.13	1.15 [−10.80, 13.11]
O.Th (μm)	15.72 ± 11.15	11.51 ± 8.42	−4.22 [−8.51, 0.08]
MLt (days)	1856.59 ± 1811.57	852.48 ± 1981.68	−934.53 [−2425.50, 556.45]

Mean ± SD
a) Mean [95% CI]

The incidence of adverse events was 100% (17 of 17 of patients). Table 52 shows the incidence of adverse events reported in ≥3 patients. Adverse drug reactions were observed in 41.2% (7 of 17) of patients, which were injection site reaction/injection site swelling/vitamin D deficiency/hyperphosphataemia, vitamin D deficiency, hyperphosphataemia, injection site pain, dysgeusia, injection site reaction, and rash in 1 patient each.

Table 52. Adverse events reported in ≥3 patients (Study UX023T-CL201, safety analysis population)

Event	Burosumab (n =17)
All events	100 (17)
Pain in extremity	52.9 (9)
Upper respiratory tract infection	47.1 (8)
Arthralgia	41.2 (7)
Cough	41.2 (7)
Nasopharyngitis	29.4 (5)
Musculoskeletal pain	29.4 (5)
Back pain	23.5 (4)
Muscle spasms	23.5 (4)
Procedural pain	23.5 (4)
Pain	23.5 (4)
Neoplasm progression	23.5 (4)
Nausea	23.5 (4)
Bronchitis	17.6 (3)
Urinary tract infection	17.6 (3)
Fall	17.6 (3)
Peripheral swelling	17.6 (3)
Nasal congestion	17.6 (3)
Respiratory tract congestion	17.6 (3)

Incidence % (number of patients), MedDRA ver. 18.1

Death occurred in 1 patient (cardiac arrest), but its causal relationship to the study drug was ruled out. Serious adverse events were observed in 6 patients, which were neoplasm progression in 4 patients, cardiac arrest/tumour compression/Pickwickian syndrome/acute respiratory failure/cholangitis/pancreatitis/septic shock, tooth abscess, and sialoadenitis in 1 patient each. A causal relationship to the study drug was ruled out for all events. An adverse event leading to treatment discontinuation (neoplasm progression) was observed in 1 patient, and its causal relationship to the study drug was ruled out.

There were no patients who turned positive for the anti-burosumab antibody during the study period.

Vital signs and electrocardiogram did not show any clinically significant changes.

7.3 Phase III studies

7.3.1 Placebo-controlled, double-blind study in adult patients with XLH (5.3.5.1-1 and 5.3.5.1-2, Study UX023-CL303 [ongoing since October 2015 (data cut-off June 2017)])

A placebo-controlled, randomized double-blind, parallel-group study in Japanese and non-Japanese[34)] adult patients with XLH (target sample size, 120 subjects; 60 in the placebo group, 60 in the burosumab group) was conducted to investigate the efficacy and safety of burosumab [for pharmacokinetic and pharmacodynamic results, see Section “6.2.1.3 Global phase III study”].

The main inclusion criteria were adult patients[35)] with XLH who met all of the following criteria: (1) At the pretreatment test, *PHEX* gene mutation was detected in the patient or a consanguineous family member with appropriate X-linked inheritance, or serum FGF23 concentration was >30 pg/mL; (2) serum phosphorus concentration at the second pretreatment test (1 day before the start of study drug administration)[36)] was <2.5 mg/dL; and (3) at the first pretreatment test (2-4 weeks before the start of

34) US, UK, France, Korea, Ireland, and Italy
35) Diagnosis of XLH was made based on the typical clinical symptoms (dwarfism, bowing of leg, etc.) as the confirmatory evidence.
36) The patient was instructed to visit the hospital after overnight fasting (≥8 hours).

the study drug administration), the patient had bone pain due to XLH/osteomalacia which was defined by BPI-Q3[37] score of ≥4. Patients were excluded if they took vitamin D, its metabolites, related drugs, or oral phosphate within 14 days before the second pretreatment test.

The study consisted of a screening period (2-4 weeks), a placebo-controlled period (24 weeks), a treatment continuation period (24 weeks), and a treatment extension period (48 weeks).[38]

During the placebo-controlled period, placebo or burosumab (1 mg/kg) was administered subcutaneously once every 4 weeks. During the treatment continuation period and the treatment extension period, burosumab (1 mg/kg) was administered subcutaneously once every 4 weeks. The dose of the study drug was calculated from the baseline body weight and rounded to the nearest 10 mg, and the maximum dose was 90 mg. If serum phosphorus concentration exceeded 5.0 mg/dL even once, the treatment was unblinded and the dose was halved. If serum phosphorus concentration was >4.5 mg/dL, the upper limit of normal, and ≤5.0 mg/dL, only when serum phosphorus concentration exceeded the upper limit of normal twice, the study drug assignment was unblinded and the dose was halved. The timing and extent of a stepwise dose increase after dose reduction were to be determined based on the discussion among the investigator and the medical experts selected by the sponsor. The study drug was administered to the abdomen, the upper arm, or the thigh, each time at a different site from the previous one. The injection volume was <1.5 mL per site. If the injection volume exceeded 1.5 mL, the study drug was injected to multiple sites.

All of the 134 randomized patients (66 in the placebo group [including 5 Japanese], 68 in the burosumab group [including 6 Japanese]) were included in the safety analysis population and the primary analysis population. During the placebo-controlled period, 1 patient in the burosumab group discontinued the study (consent withdrawal). All 133 patients who completed the placebo-controlled period (66 in the placebo group, 67 in the burosumab group) proceeded to the treatment continuation period. During the treatment continuation period, 7 patients discontinued the study (discontinuation or refusal of renewed agreement at the protocol revision in 5 patients, consent withdrawal in 1 patient, pregnancy during the study in 1 patient). A total of 126 patients who completed the treatment continuation period proceeded to the treatment extension period, and 1 patient discontinued the study (for an unidentified reason) before the data cut-off (when all patients completed the 48-week treatment with the study drug).

Table 53 shows the percentages of patients achieving mean serum phosphorus above the lower limit of normal (2.5 mg/dL) at the midpoint (Weeks 2, 6, 10, 14, 18, and 22) of each treatment cycle between baseline and Week 24, the primary efficacy endpoint. In the entire population, the percentage was higher in the burosumab group than in the placebo group (P <0.0001, Cochran-Mantel-Haenszel test adjusted for the stratification factors [BPI-Q3 score and region] used for randomization, two-sided significance level of 5%).

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[37] A self-reported, pain-specific PRO with a recall period of 24 hours used for the assessment of pain in diseases and conditions such as cancer-associated bone pain, musculoskeletal pain, and osteoarthritis. Severity of pain (worst, minimum, average, and current) and the effect on functions (general activities, gait, work, mood, enjoyment of life, relationships with other people, and sleep interference by pain) is evaluated. In BPI-Q3, the worst pain was scored on a scale of 0 (no pain at all) to 10 (the worst pain imaginable).

[38] Patients at the study sites in the US were to undergo another treatment extension period of 53 weeks at the maximum.

Table 53. Results of the primary endpoint (Study UX023-CL303 [placebo-controlled period (Week 24)], primary analysis population)

Endpoint	Entire population		Japanese subpopulation	
	Placebo	Burosumab	Placebo	Burosumab
Percentage of patients achieving mean serum phosphorus above the lower limit of normal (2.5 mg/dL) at the midpoint of each treatment cycle	5/66 7.6 [3.3, 16.5]	64/68 94.1 [85.8, 97.7]	0/5 0 [0, 43.4]	6/6 100 [61.0, 100]

Upper row, Number of patients (patients achieving the endpoint/patients evaluated); Lower row, Percentage [95% CI]

Tables 54 and 55 show the results of the main secondary endpoints in the placebo-controlled period and the treatment continuation period.

Table 54. Results of main secondary endpoints (Study UX023-CL303 [placebo-controlled period (Week 24) + treatment continuation period (Week 24)], primary analysis population)

Endpoint	Evaluation time point	Entire population		Japanese subpopulation	
		Placebo/ burosumab (n = 66)	Burosumab/ burosumab (n = 68)	Placebo/ burosumab (n = 5)	Burosumab/ burosumab (n = 6)
The worst pain score in BPI-Q3	Baseline[a)]	6.54 ± 1.43	6.81 ± 1.31	5.55 ± 1.44	6.45 ± 2.13
	Week 24[b)]	6.09 ± 2.01[c)]	5.82 ± 1.92[d)]	4.03 ± 2.07	5.54 ± 2.32
		−0.42 ± 0.22[c)]	−0.98 ± 0.19[d)]	−1.53 ± 1.36	−0.91 ± 1.68
	Week 48[b)]	4.91 ± 2.13	5.56 ± 1.90[e)]	4.20 ± 1.51	5.15 ± 2.35
		−1.64 ± 1.85	−1.26 ± 1.72[e)]	−1.35 ± 0.31	−1.31 ± 1.74
Stiffness score in WOMAC	Baseline[a)]	61.36 ± 20.77	64.71 ± 20.25	37.50 ± 23.39	66.67 ± 25.82
	Week 24[b)]	60.38 ± 21.83[c)]	53.73 ± 20.76[e)]	35.00 ± 18.54	45.83 ± 29.23
		−0.77 ± 2.70[c)]	−10.63 ± 2.99[e)]	−2.50 ± 24.04	−20.83 ± 15.14
	Week 48[b)]	44.70 ± 22.47	45.27 ± 21.90[e)]	22.50 ± 16.30	43.75 ± 25.92
		−16.67 ± 25.03	−19.32 ± 25.21[e)]	−15.00 ± 29.84	−22.92 ± 28.96
Physical function score in WOMAC	Baseline[a)]	43.89 ± 19.94	50.79 ± 19.66	18.82 ± 15.12	38.73 ± 24.03
	Week 24[b)]	42.65 ± 22.76[c)]	43.43 ± 19.51[e)]	18.82 ± 14.54	34.56 ± 21.22
		−0.97 ± 1.83[c)]	−6.90 ± 1.89[e)]	−0.00 ± 7.92	−4.17 ± 11.41
	Week 48[b)]	34.74 ± 22.62	38.35 ± 18.61[e)]	18.24 ± 16.26	27.94 ± 15.62
		−9.16 ± 18.11	−11.96 ± 15.07[e)]	−0.59 ± 12.24	−10.78 ± 13.82

a) Mean ± SD
b) Upper row, Mean ± SD; Lower row, Mean ± SD of change from baseline
c) n = 65, d) n = 67, e) n = 66

Table 55. Results of serum phosphorus concentration (Study UX023-CL303 [placebo-controlled period (Week 24) + treatment continuation period (Week 24)], primary analysis population)

Endpoint	Evaluation time point	Entire population		Japanese subpopulation	
		Placebo/ burosumab (n = 66)	Burosumab/ burosumab (n = 68)	Placebo/ burosumab (n = 5)	Burosumab/ burosumab (n = 6)
Serum phosphorus concentration (mg/dL)	Baseline[a)]	1.92 ± 0.32	2.03 ± 0.30	1.90 ± 0.16	2.03 ± 0.31
	Mean of value at the midpoint in each cycle up to Week 24[b)]	2.08 ± 0.30	3.24 ± 0.53	1.92 ± 0.19	3.29 ± 0.71
		0.16 ± 0.27	1.21 ± 0.51	0.02 ± 0.19	1.26 ± 0.77
	Mean of value at the end of each cycle up to Week 24[b)]	2.05 ± 0.30	2.72 ± 0.45	2.02 ± 0.26	2.85 ± 0.69
		0.15 ± 0.35	0.49 ± 0.40	0.12 ± 0.22	0.82 ± 0.75
	Mean of value at the midpoint in each cycle up to Week 48[b)]	3.24 ± 0.55	3.02 ± 0.48[c)]	2.99 ± 0.43	2.93 ± 0.55
		1.32 ± 0.51	0.99 ± 0.47[c)]	1.09 ± 0.39	0.89 ± 0.57
	Mean of value at the end of each cycle up to Week 48[b)]	2.47 ± 0.49	2.47 ± 0.46[d)]	2.56 ± 0.39	2.45 ± 0.37
		0.75 ± 0.44	0.54 ± 0.42[d)]	0.66 ± 0.36	0.42 ± 0.43

a) Mean ± SD
b) Upper row, Mean ± SD; Lower row, Mean ± SD of change from baseline
c) n = 66, d) n = 63

The incidence of adverse events during the placebo-controlled period was 92.4% (61 of 66 of patients) in the placebo group and 94.1% (64 of 68 of patients) in the burosumab group. The incidence of adverse drug reactions was 39.4% (26 of 66 of patients) in the placebo group and 44.1% (30 of 68 of patients)

in the burosumab group. Table 56 shows the incidences of adverse events and adverse drug reactions reported in ≥10% of patients in either group. In the Japanese subpopulation, adverse events were observed in 3 of 5 patients in the placebo group and in 6 of 6 patients in the burosumab group. The observed adverse events were nasopharyngitis/headache, tooth fracture/conjunctival deposit/back pain, blood parathyroid hormone increased/vitamin D deficiency/contusion/road traffic accident/skin abrasion/pericoronitis, pharyngitis/miliaria/vertigo, nasopharyngitis, and injection site reaction/malaise/blood phosphorus increased in 1 patient each. All of them were non-serious. Injection site reaction/blood phosphorus increased observed in the burosumab group were assessed as adverse drug reactions.

Table 56. Incidences of adverse events and adverse drug reactions reported in ≥10% of patients in either group
(Study UX023-CL303, placebo-controlled period [Week 24], safety analysis population)

Event	Placebo (n = 66)		Burosumab (n = 68)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
All events	92.4 (61)	39.4 (26)	94.1 (64)	44.1 (30)
Back pain	9.1 (6)	3.0 (2)	14.7 (10)	1.5 (1)
Nasopharyngitis	9.1 (6)	0 (0)	13.2 (9)	0 (0)
Tooth abscess	7.6 (5)	0 (0)	13.2 (9)	0 (0)
Headache	7.6 (5)	1.5 (1)	13.2 (9)	2.9 (2)
Restless legs syndrome	6.1 (4)	6.1 (4)	11.8 (8)	11.8 (8)
Nausea	9.1 (6)	3.0 (2)	10.3 (7)	4.4 (3)
Dizziness	6.1 (4)	3.0 (2)	10.3 (7)	1.5 (1)
Arthralgia	24.2 (16)	6.1 (4)	8.8 (6)	1.5 (1)
Pain in extremity	15.2 (10)	1.5 (1)	7.4 (5)	1.5 (1)
Oropharyngeal pain	10.6 (7)	1.5 (1)	1.5 (1)	0 (0)

Incidence % (number of patients), MedDRA ver. 18.1

During the entire study period up to the data cut-off, the incidence of adverse events was 95.5% (63 of 66) in patients in the placebo/burosumab group [39)] and 100% (68 of 68) in patients in the burosumab/burosumab group, and the incidence of adverse drug reactions was 48.5% (32 of 66) in patients in the placebo/burosumab group and 61.8% (42 of 68) in patients in the burosumab/burosumab group. Table 57 shows adverse events and adverse drug reactions reported in ≥10% of patients in either group. Among the Japanese patients, the incidence of adverse events was 100% (5 of 5) in patients in the placebo/burosumab group and 100% (6 of 6) in patients in the burosumab/burosumab group. Events reported in ≥2 patients in the placebo/burosumab group or the burosumab/burosumab group were nasopharyngitis in 5 patients and headache in 2 patients in the burosumab/burosumab group, none of which were serious. Adverse drug reactions were observed in 2 patients in the placebo/burosumab group (blood 1,25-dihydroxycholecalciferol increased and injection site pruritus) and in 2 patients in the burosumab/burosumab group (blood phosphorus increased/injection site reaction and injection site pruritus).

39) Events that occurred after the start of burosumab administration

Table 57. Incidences of adverse events and adverse drug reactions reported in ≥10% of patients in either group
(Study UX023-CL303, entire period up to data cut-off; safety analysis population)

Event	Placebo/burosumab[a)] (n = 66)		Burosumab/burosumab (n = 68)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
All events	95.5 (63)	48.5 (32)	100 (68)	61.8 (42)
Nasopharyngitis	15.2 (10)	0 (0)	29.4 (20)	1.5 (1)
Headache	13.6 (9)	0 (0)	26.5 (18)	2.9 (2)
Arthralgia	22.7 (15)	1.5 (1)	25.0 (17)	1.5 (1)
Tooth abscess	4.5 (3)	0 (0)	22.1 (15)	0 (0)
Fatigue	9.1 (6)	1.5 (1)	17.6 (12)	4.4 (3)
Back pain	16.7 (11)	6.1 (4)	16.2 (11)	2.9 (2)
Musculoskeletal pain	6.1 (4)	3.0 (2)	14.7 (10)	0 (0)
Vitamin D deficiency	6.1 (4)	0 (0)	14.7 (10)	0 (0)
Pain in extremity	9.1 (6)	3.0 (2)	13.2 (9)	1.5 (1)
Restless legs syndrome	9.1 (6)	7.6 (5)	13.2 (9)	13.2 (9)
Pain	9.1 (6)	3.0 (2)	13.2 (9)	4.4 (3)
Toothache	9.1 (6)	0 (0)	13.2 (9)	2.9 (2)
Diarrhoea	4.5 (3)	1.5 (1)	13.2 (9)	0 (0)
Nausea	6.1 (4)	1.5 (1)	11.8 (8)	4.4 (3)
Upper respiratory tract infection	3.0 (2)	0 (0)	11.8 (8)	0 (0)
Dizziness	3.0 (2)	0 (0)	11.8 (8)	1.5 (1)
Myalgia	3.0 (2)	0 (0)	10.3 (7)	2.9 (2)
Injection site reaction	6.1 (4)	6.1 (4)	10.3 (7)	10.3 (7)
Procedural pain	6.1 (4)	0 (0)	10.3 (7)	0 (0)
Depression	3.0 (2)	1.5 (1)	10.3 (7)	1.5 (1)

Incidence % (number of patients), MedDRA ver. 18.1
a) Events that occurred after the start of burosumab administration

No death was reported during the entire study period up to the data cut-off. There was a report of death due to road traffic accident after data cut-off in 1 patient in the burosumab/burosumab group, but its causal relationship of the death to the study drug was ruled out. During the placebo-controlled period, serious adverse events were observed in 2 patients in the placebo group (upper respiratory tract infection and invasive ductal breast carcinoma) and in 2 patients in the burosumab group (irritable bowel syndrome and back pain), but a causal relationship to the study drug was ruled out for all events. During the treatment continuation period, serious adverse events were observed in 8 patients in the placebo/burosumab group (presyncope, palpitations, arthralgia, cervical spinal stenosis, joint range of motion decreased, periodontal disease, pseudarthrosis, and subdural haematoma) and in 5 patients in the burosumab/burosumab group (cholelithiasis, colitis, procedural nausea/procedural vomiting, spinal column stenosis/myelopathy, and musculoskeletal pain). Other serious adverse events observed during the entire study period through the data cut-off were cholelithiasis, arthralgia, and joint range of motion decreased in 1 patient each, and a causal relationship to the study drug was ruled out for all events. There were no adverse events leading to treatment discontinuation. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation among Japanese patients.

There were no patients who turned positive for the anti-burosumab antibody during the study period.

Vital signs and 12-lead electrocardiogram did not show any clinically significant differences between the burosumab group and the placebo group.

7.3.2 Open-label study on the effect on osteomalacia in adult patients with XLH (5.3.5.2-4, Study UX023-CL304 [ongoing since December 2015 (data cut-off August 2017)])

An open-label, uncontrolled study in Japanese and non-Japanese[40)] adult patients with XLH (target sample size, 14 subjects) was conducted to investigate the efficacy in osteomalacia and safety of burosumab [for the results of pharmacokinetics and pharmacodynamics, see Section "6.2.1.4 Global phase III study"].

The main inclusion criteria were adult patients with XLH[35)] who met all of the following criteria: (1) At the pretreatment test, *PHEX* gene mutation was detected in the patient or a consanguineous family member with appropriate X-linked inheritance, or serum FGF23 concentration was >30 pg/mL; (2) serum phosphorus concentration was <2.5 mg/dL at the pretreatment test[36)]; and (3) at the pretreatment test, the patient had bone pain caused by XLH/osteomalacia which is defined as BPI-Q3[37)] score of ≥4. Patients were excluded if they took vitamin D, its metabolites, related drugs, or oral phosphate within 2 years before the pretreatment test.

The study consisted of a screening period (4 weeks), an open-label treatment period (48 weeks), and a treatment extension period (48 weeks).

Burosumab (1 mg/kg) was administered subcutaneously once every 4 weeks. The dose was calculated from the baseline body weight and rounded to the nearest 10 mg, and the maximum dose was 90 mg. If serum phosphorus concentration exceeded 5.0 mg/dL even once, the dose was halved. If serum phosphorus concentration was >4.5 mg/dL, the upper limit of normal, and ≤5.0 mg/dL, the dose was halved only when the second value of serum phosphorus concentration exceeded the upper limit of normal. The timing and extent of dose escalation after the dose reduction was to be determined based on the discussion made by the investigator with the medical experts selected by the sponsor. If the body weight increased by >20% from baseline, the dose was recalculated based on the new body weight. The study drug was administered to the abdomen, the upper arm, or the thigh, each time at a different site from the previous one. The injection volume was <1.5 mL per site. If the injection volume exceeded 1.5 mL, the study drug was injected to multiple sites.

All of the 14 patients (including 4 Japanese) receiving the study drug were included in the safety analysis population. Of these, 11 patients (including 1 Japanese) with available baseline and Week 48 bone biopsy data were included in the primary analysis population. Of 14 patients receiving the study drug, 1 discontinued the study (consent withdrawal) and 13 completed the open-label treatment period (48 weeks) and were still being treated with the study drug as of the data cut off data (the time point when all patients completed the 48-week treatment with the study drug).

The efficacy study showed that OV/BV[41)] (mean ± SD) was 26.12% ± 12.36% at baseline and 11.85% ± 6.60% at Week 48. The rate of change from baseline in OV/BV Week 48, the primary efficacy endpoint, was −14.9% ± 10.97%. The rate of change in OV/BV from baseline to Week 48 in individual patients

40) US and France

41) The cumulative amount of the osteoid tissue was calculated as the percentage of the total bone mass. After labeling with tetracycline or demeclocycline 3 and 1 week before, the iliac bone was biopsied and subjected to the measurement.

was −31.2% to −83.6%. The percentage of patients achieving mean serum phosphorus above the lower limit of normal (2.5 mg/dL) at the midpoint of each treatment cycle during the 24-week treatment period was one of the secondary efficacy endpoints. The value was 92.9% (13 of 14 of patients). In the Japanese subpopulation, OV/BV at baseline in 1 of 4 patients was 11%, and OV/BV at Week 48, in another patient was 18.6%. Serum phosphorus concentration at baseline and at Week 48 in each patient was 2.4 and 2.6 mg/dL, 1.2 and 2.0 mg/dL, 2.0 and 2.1 mg/dL,[42)] and 2.2 and 2.4 mg/dL, respectively.

The incidence of adverse events was 100% (14 of 14 of patients). Table 58 shows the incidences of adverse events reported in ≥3 patients. Adverse drug reactions were observed in 71.4% (10 of 14) of patients. Adverse drug reactions reported in ≥2 patients were injection site urticaria in 3 patients (21.4%), abdominal pain, asthenia, injection site pain, and injection site reaction in 2 patients (14.3%) each. In the Japanese subpopulation, adverse events were observed in all of the 4 patients (abdominal discomfort/abdominal pain upper/mouth ulceration/contusion/nasopharyngitis/bradycardia/procedural pain/pain/application site rash, constipation/periodontitis/insomnia, back pain/vitamin D deficiency/pharyngitis, and influenza like illness/injection site reaction/urticaria in 1 patient each). Adverse drug reactions were observed in 2 patients (mouth ulceration, injection site reaction/urticaria in 1 patient each), but none of them were serious.

Table 58. Adverse events reported in ≥3 patients (Study UX023-CL304, safety analysis population)

Event	Burosumab (n = 14)
All events	100 (14)
Procedural pain	50.0 (7)
Pain	35.7 (5)
Arthralgia	35.7 (5)
Tooth abscess	28.6 (4)
Back pain	28.6 (4)
Muscle spasms	28.6 (4)
Nasopharyngitis	21.4 (3)
Injection site urticaria	21.4 (3)
Fall	21.4 (3)
Bone pain	21.4 (3)
Osteoarthritis	21.4 (3)
Constipation	21.4 (3)
Hypoaesthesia	21.4 (3)
Paraesthesia	21.4 (3)
Sinus congestion	21.4 (3)
Insomnia	21.4 (3)

Incidence % (number of patients), MedDRA ver. 18.1

No death occurred. Serious adverse events were observed in 2 patients (paraesthesia and migraine in 1 patient each), but a causal relationship to the study drug was ruled out. No serious adverse events were observed in Japanese patients. There were no adverse events leading to treatment discontinuation.

Baseline anti-burosumab antibody was positive in 4 patients, while there were no patients who turned antibody-positive after the start of treatment with burosumab.

42) Value at Week 36 (value at Week 48 was not measured.)

Vital signs did not show any clinically significant changes. A clinically significant abnormality in electrocardiogram was observed in 1 patient at Week 24. The electrocardiogram at Week 48 was also abnormal but considered not to be clinically significant.

7.3.3 Open-label comparative study in pediatric patients with XLH (5.3.5.1-3, Study UX023-CL301 [ongoing since September 2016 (data cut-off July 2018)])

A randomized, open-label study in Japanese and non-Japanese[43)] pediatric patients with XLH (target sample size, 60 subjects) was conducted to investigate the efficacy and safety of burosumab, using the treatment with oral phosphate and active vitamin D as the control [for the results of pharmacokinetics and pharmacodynamics, see Section "6.2.2.2 Global phase III study"].

The main inclusion criteria were pediatric patients aged ≥1 and ≤12 years with XLH who met all of the following criteria: (a) radiographic features of rickets with total RSS[28)] score ≥2.0 by the central assessment; (b) *PHEX* gene mutation was detected in the patient or a consanguineous family member with X-linked inheritance; (c) serum phosphorus concentration was <3.0 mg/dL both at the pretreatment test and at the baseline visit[27)]; and (d) the patient used oral phosphate and active vitamin D[44)] ≥7 days before the baseline visit.

The study consisted of a screening period (8 weeks at the maximum), a study drug treatment period (64 weeks), and a treatment continuation period[45)] (76 weeks).

During the study drug treatment period, burosumab (0.8 mg/kg) was administered subcutaneously once every 2 weeks, or oral phosphate and active vitamin D, adjusted for each patient by the investigator, were administered. The dose of burosumab could be increased to 1.2 mg/kg if the patient met all of the following criteria: (a) serum phosphorus concentration was below the lower limit of normal for the patient's age in 2 consecutive measurements; (b) the increase in serum phosphorus concentration from baseline was ≤0.5 mg/dL by the most recent measurement; and (c) the low serum phosphorus concentration was not due to missed study drug administration. The dose was calculated based on the body weight measured most recently before administration, and the maximum dose was 90 mg. The study drug was administered to the abdomen, the upper arm, the thigh, or the hip, each time at a different site from the previous one. During the treatment continuation period, patients who had been assigned to the burosumab group during the study drug treatment received the same dose as that in the study drug treatment period, and patients who had been assigned to the control group received burosumab according to the same dosage regimen as that in the burosumab group during the study drug treatment period.

All of the 61 randomized patients (29 in the burosumab group [including 2 Japanese], 32 in the control group [including 3 Japanese]) were included in the safety analysis population and FAS, and the FAS was used as the primary efficacy analysis population. All patients receiving the study drug completed the study drug treatment period, and 25 patients in the burosumab group and 26 patients in the control

43) US, Canada, UK, Australia, Korea, and Sweden
44) Patients aged ≥3 years were required to have used the drugs for ≥12 months, and patients aged <3 years for ≥6 months.
45) The treatment continuation period was not included in Japan and Korea.

group proceeded to the treatment continuation period at the data cut-off (when all patients completed the 64-week treatment with the study drug).

Difference in radiographic global impression of change (RGI-C) global score[29] at Week 40, the primary efficacy endpoint, between the burosumab group and the placebo group [95% CI] was 1.14 [0.83, 1.45], showing a statistically significant improvement in the burosumab group than in the placebo group (P <0.0001, an analysis of covariance using baseline rickets severity and age as the covariates, two-sided significance level of 5%).

Table 59 shows the results of the primary endpoint and the main secondary endpoints.

Table 59. Results of the primary endpoint and the main secondary endpoints (Study UX023-CL301, study drug treatment period [Week 64], FAS)

Endpoint		Evaluation time point	Burosumab (n = 29)	Control (n = 32)
RGI-C score	Global score	Week 40[a), b)]	+1.92 ± 0.11	+0.77 ± 0.11
		Week 64[a), c)]	+2.06 ± 0.07	+1.03 ± 0.14
	Wrist score	Week 40[a), b)]	+2.07 ± 0.15	+0.76 ± 0.15
		Week 64[a), c)]	+2.14 ± 0.12	+0.99 ± 0.14
	Knee score	Week 40[a), b)]	+1.83 ± 0.10	+0.71 ± 0.10
		Week 64[a), c)]	+2.03 ± 0.06	+1.03 ± 0.14
	Long leg score	Week 40[a), b)]	+0.62 ± 0.12	+0.21 ± 0.12
		Week 64[a), c)]	+1.25 ± 0.17	+0.29 ± 0.12
Supine or standing height Z-score		Baseline[d)]	−2.32 ± 1.17[g)]	−2.05 ± 0.87
		Week 40[c), e)]	−2.12 ± 1.22	−2.02 ± 0.85
			0.16 ± 0.05	0.03 ± 0.03
		Week 64[c), e)]	−2.11 ± 1.11	−2.03 ± 0.83
			0.17 ± 0.07	0.02 ± 0.04
Total RSS score		Baseline[d)]	3.16 ± 0.99[g)]	3.19 ± 1.14
		Week 40[b), e)]	1.13 ± 0.72[g)]	2.47 ± 1.09
			−2.04 ± 0.15	−0.71 ± 0.14
		Week 64[c), e)]	0.95 ± 0.72	2.17 ± 0.95
			−2.23 ± 0.12	−1.01 ± 0.15
Serum phosphorus concentration (mg/dL)		Baseline[d)]	2.42 ± 0.24	2.30 ± 0.26
		Week 40[f)]	3.30 ± 0.43	2.53 ± 0.34
			0.88 ± 0.42	0.23 ± 0.39
		Week 64[f)]	3.29 ± 0.42	2.54 ± 0.39
			0.87 ± 0.43	0.24 ± 0.36
Serum ALP concentration (U/L)		Baseline[d)]	510.76 ± 124.90	523.44 ± 154.42
		Week 40[f)]	380.76 ± 99.46	488.69 ± 189.07
			−130.00 ± 78.38	−34.75 ± 99.07
		Week 64[f)]	336.86 ± 86.13	495.41 ± 182.07
			−173.90 ± 89.12	−28.03 ± 116.66

a) Least squares mean ± SE
b) Calculated using the covariance analysis model
c) Calculated by generalized estimating equation using the data obtained from measurements over time.
d) Mean ± SD
e) Upper row, Mean ± SD; Lower row, Least squares mean ± SE of change from baseline
f) Upper row, Mean ± SD; Lower row, Mean ± SD of change from baseline
g) n = 28

Figure 4 shows changes in serum phosphorus concentration over time.

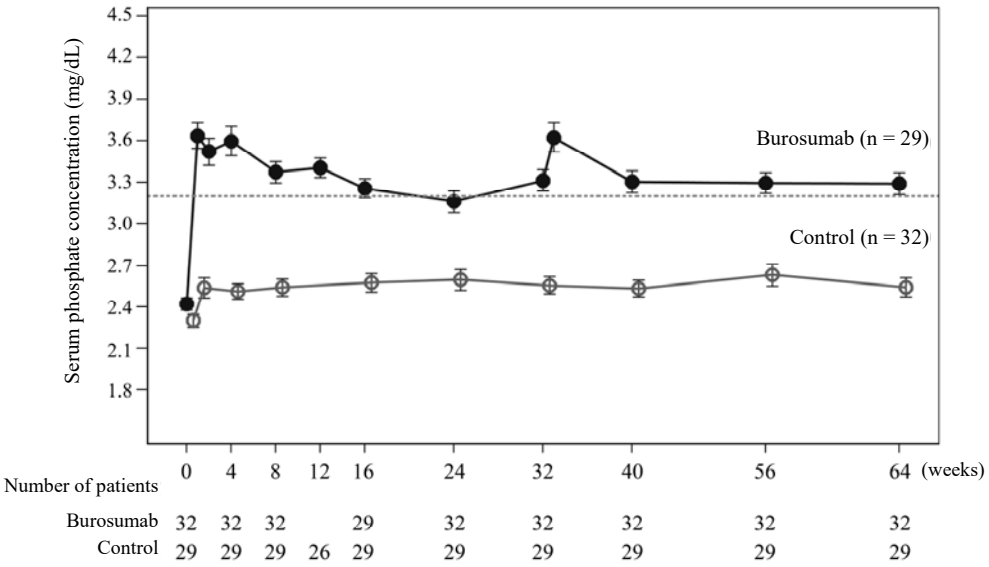

Figure 4. Changes in serum phosphorus concentration over time through Week 64 (Study UX023-CL301; efficacy analysis population, mean ± SE)

Table 60 shows the characteristics of Japanese patients (2 in the burosumab group, 3 in the control group), and Table 61 shows the results of the efficacy endpoints.

Table 60. Characteristics of individual patients[a] (Study UX023-CL301, Japanese subpopulation)

	Burosumab		Control		
	Patient code number				
	1	2	3	4	5
Sex	Male	Male	Female	Male	Male
Age (years)	1.8	10.6	7.4	11.8	10.4
Standing height	77.00	124.90	112.90	132.70	125.00
Height Z score	−2.77	−2.58	−2.25	−2.25	−2.47
Body weight (kg)	9.79	22.90	21.20	38.40	30.60

a) Baseline (at screening visit [within 8 weeks before the start of the study drug administration])

Table 61. Results of efficacy endpoints in individual patients (Study UX023-CL301, Japanese subpopulation)

Endpoint			Patient number				
		Evaluation time point	1	2	3	4	5
RGI-C score	Global score	Week 40	+1	+1	+1.3	+1	0
		Week 64	+1.3	+1	+1.3	+1	+1
	Long leg score	Week 40	−0.3	0	0	0	−0.7
		Week 64	+1	0	0	0	+0.7
	Wrist score	Week 40	+1	+1	0	−0.7	0
		Week 64	+1.3	+1	+1	+0.3	+0.7
	Wrist score	Week 40	+0.7	+1	+1.3	+1	0
		Week 64	+1.3	+1.3	+1.3	+1	+1
Supine or standing height Z-score		Baseline	−2.77	−2.58	−2.25	−2.25	−2.47
		Week 24	−2.92	−2.49	−2.20	−2.18	−2.33
		Week 40	−3.26	−2.50	−2.21	−2.09	−2.20
		Week 64	−3.46	−2.48	−1.99	−2.02	−2.10
Total RSS score		Baseline	6.5	2	2	2.5	3
		Week 40	4	1.5	0.5	3	3.5
		Week 64	3.5	1	0.5	2	2.5
Serum phosphorus concentration (mg/dL)		Baseline	2	2.4	2.4	2.5	2.0
		Week 1	2.4	2.8	2.4	2.8	2.1
		Week 2	2.6	2.8	-	-	-
		Week 4	2.6	3.3	2.8	2.6	3.3
		Week 8	2.5	3.1	2.7	2.8	2.0
		Week 16	2.5	2.5	2.7	2.7	2.0
		Week 24	2.5	2.8	2.5	2.6	2.0
		Week 40	2.2	3.0	2.6	2.8	2.4
		Week 52	2.7	2.9	2.5	2.6	2.5
		Week 64	2.5	2.8	2.8	2.8	1.9
Serum ALP concentration (U/L)		Baseline	570	430	520	559	1179
		Week 40	378	391	435	841	1356
		Week 64	275	285	421	824	1304

The incidence of adverse events during the study drug treatment period was 100% (29 of 29 of patients) in the burosumab group and 84.4% (27 of 32 of patients) in the control group, and the incidence of adverse drug reactions was 58.6% (17 of 29 of patients) in the burosumab group and 21.9% (7 of 32 of patients) in the control group. Table 62 shows the incidences of adverse events and adverse drug reactions reported in ≥10% of patients in either group. Among the Japanese subpopulation, adverse events were observed in 2 patients in the burosumab group (fistula/pyrexia/diarrhoea/hand-foot-and-mouth disease/periodontitis/upper respiratory tract infection and nasopharyngitis/dry skin/seasonal allergy/influenza in 1 patient each) and in 1 patient in the control group (malocclusion). None of these adverse events were serious, and a causal relationship to the study drug was ruled out for all events.

Table 62. Adverse events and adverse drug reactions with an incidence of ≥10% in either group (Study UX023-CL301, Week 64 of administration; safety analysis population)

Event	Burosumab (n = 29)		Control (n = 32)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
All events	100 (29)	58.6 (17)	84.4 (27)	21.9 (7)
Pyrexia	55.2 (16)	0 (0)	18.8 (6)	0 (0)
Cough	51.7 (15)	0 (0)	18.8 (6)	0 (0)
Arthralgia	44.8 (13)	20.7 (6)	31.3 (10)	12.5 (4)
Vomiting	41.4 (12)	0 (0)	25.0 (8)	0 (0)
Nasopharyngitis	37.9 (11)	0 (0)	43.8 (14)	0 (0)
Pain in extremity	37.9 (11)	24.1 (7)	31.3 (10)	3.1 (1)
Headache	34.5 (10)	3.4 (1)	18.8 (6)	0 (0)
Injection site erythema	31.0 (9)	27.8 (8)	0 (0)	0 (0)
Dental caries	31.0 (9)	6.9 (2)	6.3 (2)	0 (0)
Tooth abscess	27.6 (8)	13.8 (4)	9.4 (3)	0 (0)
Diarrhoea	24.1 (7)	0 (0)	6.3 (2)	1 (3.1)
Injection site reaction	24.1 (7)	24.1 (7)	0 (0)	0 (0)
Rhinorrhoea	24.1 (7)	0 (0)	6.3 (2)	0 (0)
Vitamin D decreased	20.7 (6)	0 (0)	3.1 (1)	0 (0)
Vitamin D deficiency	17.2 (5)	0 (0)	3.1 (1)	0 (0)
Oropharyngeal pain	17.2 (5)	0 (0)	3.1 (1)	0 (0)
Constipation	17.2 (5)	0 (0)	0 (0)	0 (0)
Nasal congestion	17.2 (5)	0 (0)	3.1 (1)	0 (0)
Influenza	13.8 (4)	0 (0)	18.8 (6)	0 (0)
Seasonal allergy	13.8 (4)	0 (0)	6.3 (2)	0 (0)
Ear pain	13.8 (4)	0 (0)	3.1 (1)	0 (0)
Asthma	13.8 (4)	0 (0)	3.1 (1)	0 (0)
Toothache	13.8 (4)	3.4 (1)	3.1 (1)	0 (0)
Contusion	13.8 (4)	0 (0)	0 (0)	0 (0)
Nausea	10.3 (3)	3.4 (1)	3.1 (1)	0 (0)
Abdominal pain upper	10.3 (3)	0 (0)	9.4 (3)	0 (0)
Rash	10.3 (3)	0 (0)	6.3 (2)	0 (0)
Upper respiratory tract infection	10.3 (3)	3.4 (1)	9.4 (3)	0 (0)
Injection site pruritus	10.3 (3)	10.3 (3)	0 (0)	0 (0)
Injection site rash	10.3 (3)	10.3 (3)	0 (0)	0 (0)
Injection site swelling	10.3 (3)	10.3 (3)	0 (0)	0 (0)
Fall	10.3 (3)	0 (0)	0 (0)	0 (0)

Incidence % (number of patients), MedDRA ver. 18.1

No death was reported during the study drug treatment period. Serious adverse events were observed in 3 patients in the burosumab group (craniosynostosis, viral infection, and migraine) and in 1 patient in the control group (haematuria/craniosynostosis/knee deformity), but a causal relationship to the study drug was ruled out for all events. No serious adverse event was observed in Japanese patients. There were no adverse events leading to treatment discontinuation.

A total of 3 patients in the burosumab group tested positive for baseline anti-burosumab antibody. Of these, 1 patient turned antibody-negative after burosumab administration. The remaining 2 patients continued to be antibody-positive after burosumab administration. One of them tested positive at all 6 measuring time points and positive for neutralizing antibody at 2 of the 6 measurements. The other patient was positive at 2 of 6 measurements and negative for neutralizing antibody. All patients showed increased serum phosphorus concentration and improved parameters related to rachitic symptoms assessed by RGI-C and RSS scores. There were no hypersensitivity-related adverse event.

Vital signs and 12-lead electrocardiogram did not show any clinically significant changes.

7.3.4 Open-label study in Japanese pediatric patients with XLH (5.3.5.2-7, Study KRN23-003 [ongoing since July 2017 (data cut-off June 2018)])

An open-label, uncontrolled study in Japanese pediatric patients with XLH (target sample size, ≥10 subjects) was conducted to investigate the efficacy and safety of burosumab [for the results of pharmacokinetics and pharmacodynamics, see Section "6.2.2.1 Japanese phase III study"].

The main inclusion criteria were pediatric patients aged 1 to 12 years with XLH who met all of the following criteria: (a) the growth plate was open at the pretreatment test; (b) *PHEX* gene mutation was detected in the patient or a consanguineous family member with X-linked inheritance, or serum FGF23 concentration was ≥30 pg/mL at the pretreatment test; (c) the patient had rachitic changes (metaphyseal cupping, wide and fraying epiphyseal line, etc.) or clinical symptoms of rickets (knock-knees, bow-legs, etc.) confirmed by the investigator based on plain radiographic imaging at the pretreatment test, and (d) serum phosphorus concentration was <3.0 mg/dL at the pretreatment test.

The study consisted of a screening period, a treatment period (40 weeks), and a treatment extension period (44 weeks or until marketing approval, whichever came earlier).

Burosumab (0.8 mg/kg) was administered subcutaneously once every 2 weeks. After Week 6, the dose could be increased to 1.2 mg/kg if the patient met all of the following criteria: (a) serum phosphorus concentration was below the lower limit of normal for the patient's age in 2 consecutive measurements; (b) the increase in serum phosphorus concentration from baseline was ≤0.5 mg/dL by the most recent measurement; and (c) burosumab was administered appropriately as specified. If there was a safety concern because of adverse events, the dose could be reduced by 0.2 mg/kg at the discretion of the investigator, etc. If, after the dose reduction, the patient met all of the dose increase criteria (a) through (c), the dose could be increased by 0.2 mg/kg. The dose was calculated based on the body weight immediately before administration, and the maximum dose was 1.2 mg/kg. The study drug was administered to the abdomen, the upper arm, the thigh, or the hip, each time at a different site from the previous one. Self-injection within the hospital was allowed from Week 4. Self-injection at home was allowed from Week 10 if the patient experienced one or more self-injections in the hospital and was judged eligible for self-injection by the investigator.

All of the 15 patients receiving the study drug were included in the safety analysis population and FAS, and the FAS was used as the primary efficacy analysis population. All patients receiving the study drug had completed the 40-week treatment by the data cut-off date (time point when data up to Week 40 were collected from all patients).

Table 63 shows the results of the main efficacy endpoints.

Table 63. Results of main efficacy endpoints (Study KRN23-003 [Week 40], FAS)

Endpoint		Burosumab (n = 15)		
		Baseline	Week 40	Change up to Week 40
Serum phosphorus concentration (mg/dL)		2.61 ± 0.32	3.51 ± 0.45	0.90 ± 0.30
1,25(OH)$_2$D concentration (pg/mL)		24.65 ± 12.70	62.19 ± 12.50	37.53 ± 12.88
Serum ALP concentration (U/L)		1589.3 ± 366.9	1131.3 ± 263.6	−458.0 ± 288.6
TmP/GFR(mg/dL)		2.4369 ± 0.4908	3.6124 ± 0.6072	1.1755 ± 0.5221
Total RSS score		1.29 ± 1.17[a)]	0.62 ± 0.58[b)]	−0.77 ± 0.99[b)]
RGI-C score	Global score	-	-	+1.51 ± 0.80
	Knee score	-	-	+1.61 ± 0.91
	Wrist score	-	-	+1.40 ± 0.92
	Long leg score	-	-	+0.73 ± 0.85
Height Z-score		−1.651 ± 0.869	−1.694 ± 0.756	−0.043 ± 0.225
6MWT (m)		425.0 ± 81.3	437.6 ± 77.3	12.6 ± 75.5

Mean ± SD; -, Not applicable
a) n = 14, b) n = 13

The incidence of adverse events at the data cut-off was 93.3% (14 of 15 of patients). Adverse events reported in ≥2 patients were influenza and upper respiratory tract infection in 3 patients each and nasopharyngitis, dental caries, and otitis media in 2 patients each. Adverse drug reactions occurred in 13.3% (2 of 15) of patients, which were injection site pruritus and blood 25-hydroxycholecalciferol decreased in 1 patient each. In this study, all of the 15 patients self-injected the study drug, and 12 patients started self-injection at or before Week 8. After the start of self-injection, adverse events occurred in 80.0% (12 of 15) of patients. Adverse events reported in ≥2 patients were influenza and upper respiratory tract infection in 3 patients each and dental caries and otitis media in 2 patients each. An adverse drug reaction (blood 25-hydroxycholecalciferol decreased) was observed in 1 patient.

No death was reported. A serious adverse event (tonsillitis) was observed in 1 patient, but its causal relationship to the study drug was ruled out. There were no adverse events leading to treatment discontinuation.

One patient was positive for baseline anti-burosumab antibody and negative for neutralizing antibody. There were no patients who turned anti-burosumab antibody-positive after the start of burosumab administration.

Vital signs and 12-electrocardiogram did not show any clinically significant changes.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical positioning of burosumab

The applicant's explanation:

FGF23-related hypophosphatemic rickets/osteomalacia is impaired mineralization of bones and cartilages caused by the loss of phosphate from the body due to excess FGF23 production, resulting in bone fracture, pain, and gait disturbance, etc., which limit mobility. Rickets/osteomalacia is differentiated as FGF23-related hypophosphatemic rickets/osteomalacia if the patient has hypophosphataemia and blood FGF23 concentration of ≥30 pg/mL according to the diagnostic flowchart of "Manual for the diagnosis of rickets/osteomalacia" (*The Japanese journal of endocrinology*. 2015;91(suppl):1-11).

For patients with TIO with FGF23-overproducing tumor, the first-line treatment is surgical resection of the tumor. Patients with TIO ineligible for surgical operation and those with the disease caused by gene mutation are subjected to symptomatic treatment, that is, frequent administration of oral phosphate and active vitamin D_3 to supplement phosphate lost in urine. However, the conventional treatment with oral phosphate and active vitamin D_3 is fraught with widely varied serum phosphorus and calcium concentrations, which may cause adverse drug reactions such as secondary or tertiary hyperparathyroidism and kidney calcification. These adverse drug reactions preclude further use of phosphate preparation for the maintenance of serum phosphorus concentration within the normal range. Overseas guidelines for the treatment of XLH advise that the treatment with oral phosphate and active vitamin D_3 should not aim at normalizing serum phosphorus concentration (*J Bone Miner Res.* 2011;26:1381-8). According to the current guidelines, oral phosphate should preferably be administered as frequently as possible. However, the treatment often results in poor compliance and thus has limited effect.

Burosumab binds to FGF23 and inhibits intracellular signal transduction via the FGF23/Klotho/FGFR complex. Excess FGF23 is the causative factor of hypophosphataemia, which is neutralized by burosumab. Burosumab is therefore expected to serve as a radical therapeutic agent for FGF23-related hypophosphatemic rickets/osteomalacia. Burosumab, by maintaining serum phosphorus concentration within the normal range without abrupt change in serum phosphorus or calcium concentration, is expected to improve impaired mineralization of bones, growth impairment, motor function, and quality of life (QOL), without adverse drug reactions such as secondary or tertiary hyperparathyroidism and kidney calcification. Thus, it is of great significance to provide burosumab to the clinical setting.

PMDA's view:
Burosumab, with its novel action mechanism, neutralizes excess FGF23 that causes FGF23-related hypophosphatemic rickets/osteomalacia. Therefore, it is of significance to supply burosumab to the clinical setting as a treatment option for improving the symptoms of FGF23-related hypophosphatemic rickets/osteomalacia.

7.R.2 Reviewing policy on burosumab

PMDA's view:
XLH is a typical disease with excess FGF23 production caused by gene mutation. The disease is diagnosed based on clinical signs such as skeletal deformity and growth retardation, rachitic features such as metaphyseal cupping and wide and fraying epiphyseal line on plain radiographic imaging, increased serum FGF23 concentration, hypophosphatemia and excess phosphate excretion in urine in laboratory test, and a family history. There is no significant difference in the diagnostic method between Japan and foreign countries. Across the world, phosphate preparation and active vitamin D_3 formulation are often used orally as a symptomatic therapy aiming to supplement phosphate against hypophosphatemia caused by XLH. There was no significant difference in the pharmacokinetics of burosumab either in adult or pediatric patients with XLH between Japan and foreign countries [see Section "6.R.1 Comparison of pharmacokinetics and pharmacodynamics between Japanese and non-Japanese patients with XLH"]. Phase III studies in adult and pediatric patients with XLH (Studies UX023-CL303, UX023-CL304, and UX023-CL301) were all conducted as global studies. Given the

above findings, the extrinsic and intrinsic ethnic factors have only limited effects on the outcome of burosumab therapy. TIO, the acquired disease associated with excess FGF23, is confirmed by standard imaging and additional diagnostic imaging of somatostatin receptor that identifies the causative lesion in patients with no family history of FGF23-related hypophosphatemic rickets/osteomalacia who have biochemical findings such as hypophosphatemia, excess phosphate excretion in urine, and increased serum FGF23 concentration, and clinical findings such as muscle weakness and bone pain. This diagnostic method is more or less common in and outside Japan. The therapeutic approach for TIO is surgical resection of tumor lesion when it is clearly identified or treatment with oral phosphate and active vitamin D_3 when the complete resection of causative lesion is difficult, which is also common in and outside Japan in general. Furthermore, the pharmacokinetics of burosumab did not significantly differ between Japanese and non-Japanese patients with TIO [see Section "6.R.2 Comparison of pharmacokinetics and pharmacodynamics between Japanese and non-Japanese patients with TIO"]. The phase II study of burosumab (Study KRN23-002) on the efficacy and safety in patients with TIO was conducted as a global study of Japan and Korea. Results of the foreign phase II study (Study UX023T-CL201) in patients with TIO, etc., were also submitted. Given these, the extrinsic and intrinsic ethnic factors have limited effects on the outcome of burosumab therapy.

Based on the above, the efficacy and safety of burosumab are discussed in Sections "7.R.3 Efficacy" and "7.R.4 Safety," focused on the results of the global and Japanese phase III studies in adult and pediatric patients with XLH (Studies UX023-CL303, UX023-CL304, UX023-CL301, and KRN23-003) and on the global and foreign phase II studies in patients with TIO, etc. (Studies KRN23-002 and UX023T-CL201).

7.R.3 Efficacy

7.R.3.1 Efficacy in adult patients with XLH

The applicant's explanation:

In the global phase III study (Study UX023-CL303) in adult patients with XLH, the percentage [95% CI] of patients achieving mean serum phosphate above the lower limit of normal (2.5 mg/dL) at the midpoint[46)] of each treatment cycle between baseline and Week 24, the primary efficacy endpoint, was 7.6% [3.3%, 16.5%] (5 of 66) of patients in the placebo group and 94.1% [85.8%, 97.7%] (64 of 68) of patients in the burosumab group, showing a significantly higher percentage in the burosumab group than in the placebo group (Table 53). During the treatment continuation period, serum phosphorus concentration in the burosumab continuation group was maintained above the lower limit of normal through Week 48 of treatment. Similarly, in the global phase III study in adult patients with XLH (Study UX023-CL304), the percentage of patients achieving mean serum phosphorus above the lower limit of normal (2.5 mg/dL) at the midpoint[46)] of each treatment cycle between baseline and Week 24 was 92.9% (13 of 14) of patients.

According to the assessment of effect on bones based on baseline whole body bone radiography in Study UX023-CL303, fractures were "progressing (not cured)" in 12.1% (8 of 66) of patients in the placebo group and in 11.8% (8 of 68) of patients in the burosumab group, and pseudofractures were "progressing (not cured)" in 51.5% (34 of 66) of patients in the placebo group and in 42.6% (29 of 68) of patients in

46) Week 2, 6, 10, 14, 18, and 22

the burosumab group. Fractures/pseudofractures were "progressing (not cured)" in 91 sites in the placebo group and 65 sites in the burosumab group. During the study period, existing fractures/pseudofractures were classified as "unchanged," "partially cured," "cured," or "aggravated." The results showed that, among the fractures/pseudofractures assessed as "progressing (not cured)" at baseline, the percentage of fractures/pseudofractures that "cured" at each evaluation time point was 7.7% (7 of 91 sites) at Weeks 12 and 24 in the placebo group but increased to 35.2% (32 of 91 sites) at Week 48 (Week 24 after switching to burosumab). In the burosumab group, the percentage of fractures/pseudofractures assessed as "cured" increased with time (20.0% [13 of 65 sites] at Week 12, 43.1% [28 of 65] at Week 24, 63.1% [41 of 65] at Week 48). In study UX023-CL304, the rate of change in OV/BV[41] (measured by iliac crest biopsy) from baseline through Week 48, the primary endpoint, was −31.2% to −83.6%, showing a decrease. Also, osteomalacia-related other histomorphological parameters (osteoid thickness [O.Th], osteoid surface/bone surface [OS/BS], and mineralisation lag time [MLt]) showed decreases in values.

Osteomalacia-related clinical symptoms (pain reported by the patient, motor function, and physical function) were assessed based on the secondary endpoints in Study UX023-CL303, namely, change in BPI-Q3 score from baseline, changes in Western Ontario and McMaster Universities osteoarthritis index (WOMAC) physical function score, and stiffness score. The results showed a tendency toward improvement as compared with the placebo group (Table 54).

Table 64 shows the baseline patient characteristics in Studies UX023-CL303 and UX023-CL304. As compared with the entire population, the Japanese subpopulation showed lower body weight and a tendency toward smaller BMI, with no significant difference in other demographic or baseline characteristics.

Table 64. Baseline patient characteristics (Studies UX023-CL303 and UX023-CL304, FAS)

Characteristic		Study UX023-CL303				Study UX023-CL304	
		Japanese subpopulation		Entire population		Japanese subpopulation (n = 4)	Entire population (n = 14)
		Placebo (n = 5)	Burosumab (n = 6)	Placebo (n = 66)	Burosumab (n = 68)		
Age (years)		32.0 ± 14.9	42.6 ± 14.6	38.7 ± 12.8	41.3 ± 11.6	45.6 ± 6.1	40.1 ± 8.7
Sex[a)]	Male	40.0 (2)	50.0 (3)	34.8 (23)	35.3 (24)	50.0 (2)	85.7 (12)
	Female	60.0 (3)	50.0 (3)	65.2 (43)	64.7 (44)	50.0 (2)	14.3 (2)
Height (cm)		149.00 ± 10.06	148.85 ± 5.75	152.69 ± 11.84	152.15 ± 9.49	143.95 ± 10.89	150.42 ± 8.98
Body weight (kg)		50.78 ± 16.73	51.62 ± 10.49	71.27 ± 18.89	70.06 ± 19.00	58.98 ± 13.16	70.26 ± 22.00
BMI (kg/m^2)		22.47 ± 4.56	23.17 ± 3.75	30.60 ± 7.79	29.98 ± 7.49	28.31 ± 4.20	30.80 ± 8.47
Serum phosphorus concentration (mg/dL)		1.90 ± 0.16	2.03 ± 0.31	1.92 ± 0.32	2.03 ± 0.30	1.95 ± 0.53	2.24 ± 0.40

Mean ± SD

a) Percentage (%) (number of patients)

The effect of the difference in body weight on efficacy of burosumab was investigated. The results showed that the primary endpoint of Study UX023-CL303 was achieved in 9.5% (4 of 42) of patients in the placebo group and 92.3% (36 of 39) of patients in the burosumab group in the subpopulation of body weight ≥65 kg; and in 4.2% (1 of 24) of patients in the placebo group and 96.6% (28 of 29) of patients in the burosumab group in the subpopulation of body weight <65 kg, showing similar results in both subpopulations.

The above results of the clinical studies demonstrate the efficacy of burosumab in adult patients with XLH.

PMDA's view:
The primary efficacy endpoint of Study UX023-CL303 was the percentage of patients achieving mean serum phosphorus above the lower limit of normal (2.5 mg/dL) at the midpoint of each treatment cycle between baseline and Week 24. The percentage was significantly higher in the burosumab group than in the placebo group. The increased serum phosphorus level was maintained during long-term treatment. The results of Study UX023-CL304 were similar to those of the burosumab group of Study UX023-CL303. Also, osteomalacia-related histomorphological parameters, clinical symptoms (pain, motor function, and physical function), and fracture/pseudofracture findings showed a tendency toward improvement. Based on the above, efficacy of burosumab in adult patients with XLH has been demonstrated.

7.R.3.2 Efficacy in pediatric patients with XLH

The applicant's explanation:
In the global phase III study (Study UX023-CL301) in pediatric patients aged 1 to 12 years with XLH, the primary endpoint RGI-C global score[29] at Week 40 (least squares mean ± standard error) was +1.92 ± 0.11 in the burosumab group and +0.77 ± 0.11 in the control group (treated with oral phosphate and active vitamin D_3). The between-group difference [95% CI] (burosumab group – control group) was 1.14 [0.83, 1.45], showing a significant improvement in the burosumab group as compared with the control group ($P < 0.0001$, analysis of covariance with baseline rickets severity and age as the covariates, two-sided significance level of 5%). Also, all of the following main secondary endpoints showed a tendency toward improvement in the burosumab group as compared with the control group: RGI-C long leg score, supine or standing height Z-score, total RSS score,[28] change in serum phosphorus concentration from baseline, change in serum ALP concentration from baseline (Table 59). At Week 64 as well, RGI-C global score was +2.06 ± 0.07 in the burosumab group and 1.03 ± 0.14 in the control group, and results of the secondary endpoints were also similar to those at Week 40.

Table 65 shows baseline patient characteristics in the Japanese subpopulation and the entire population in Study UX023-CL301. Age and height were higher, and body weight tended to be higher, in the control group of the Japanese subpopulation than in the entire population, with no significant difference in other demographic or other baseline characteristics between the two populations.

Table 65. Baseline patient characteristics (Study UX023-CL301, FAS)

Item		Japanese subpopulation		Entire population	
		Burosumab (n = 2)	Control (n = 3)	Burosumab (n = 29)	Control (n = 32)
Age (years)		1.8, 10.6	9.87 ± 2.25	5.83 ± 3.43	6.34 ± 3.24
Sex[a)]	Male	100 (2)	66.7 (2)	44.8 (13)	43.8 (14)
	Female	0 (0)	33.3 (1)	55.2 (16)	56.3 (18)
Height (cm)		77.0, 124.9	123.53 ± 9.98	102.60 ± 20.01	106.48 ± 19.76
Body weight (kg)		9.79, 22.9	30.07 ± 8.61	19.59 ± 8.98	21.55 ± 8.91
BMI (kg/m^2)		14.68, 16.51	19.34 ± 2.60	18.00 ± 2.45	18.22 ± 2.16
Serum phosphorus concentration (mg/dL)		2.0, 2.4	2.30 ± 0.27	2.42 ± 0.24	2.30 ± 0.26

Mean ± SD, individual values in burosumab group (n = 2) of the Japanese subpopulation
a) Percentage (%) (number of patients)

Because of the limited number of Japanese patients enrolled in the study, comparison between groups of the Japanese subpopulation was less than accurate. Nevertheless, RGI-C global score and long-leg score in the burosumab group were not significantly different from those in the control group, whereas total RSS score tended to improve in the burosumab group (Table 61).

In the Japanese phase III study (Study KRN23-003) in Japanese pediatric patients aged 1 to 12 years with XLH, all RGI-C scores at Week 40 showed a tendency toward improvement (Table 63). Serum phosphorus concentration increased after the start of burosumab administration, reached the maximum level at Week 4, and remained without significant fluctuation through Week 40.

Similarly, in the foreign phase II study (Study UX023-CL205) in pediatric patients aged 1 to 4 years with XLH, serum phosphorus concentration, the primary endpoint, increased from baseline after the start of burosumab administration and was maintained through Week 40. Among secondary endpoints, total RSS score and RGI-C score showed a tendency toward improvement at Week 40 (Table 45). Supine or standing height Z-score did not show any significant effect of burosumab on growth, possibly because of low-age patients investigated and because of the short period of exposure to burosumab.

The applicant considers that these clinical study results demonstrated the efficacy of burosumab in pediatric patients with XLH.

PMDA's view:
In the global Study UX023-CL301 in pediatric patients aged 1 to 12 years with XLH, RGI-C global score at Week 40, which is the primary endpoint and an index for rachitic symptoms, showed a significant improvement in the burosumab group as compared with the control group (treated with oral phosphate and active vitamin D_3). The mean serum phosphorus concentration did not exceed the lower limit of normal in any of the time points in the control group, but it exceeded the lower limit of normal at almost all time points in the burosumab group. The results were maintained through Week 64, and the currently available data indicate that the efficacy is expected to be maintained during the long-term treatment. Similarly, in the Japanese Study KRN23-003 in Japanese pediatric patients with XLH, RGI-C global score and serum phosphorus concentration showed a tendency toward improvement at Week 40. Similar results were obtained in low-age patients. Thus, in the foreign Study UX023-CL205 in patients aged 1 to 4 years, RGI-C global score and serum phosphorus concentration improved. PMDA concluded that burosumab is effective in pediatric patients with XLH.

7.R.3.3 Efficacy in patients with TIO

The applicant's explanation:

Because of the extremely limited number of patients with TIO, a comparative study seemed infeasible. Therefore, efficacy in patients with TIO was evaluated in an uncontrolled study. In Study KRN23-002 in patients with TIO, etc., serum phosphorus concentration, the primary endpoint, increased after burosumab administration, and the mean level remained above the lower limit of normal (2.5 mg/dL) at Week 24 onward (Figure 2). Results of the secondary endpoints showed a tendency toward improvement in patient-reported outcomes (worst BPI score and motor function) (Table 48). In 3 patients with bone biopsy results, osteomalacia-related tissue morphology was severe at baseline but rated as mild in 2 patients at Week 48. ^{99m}Tc-labeled bone scan revealed fractures/pseudofractures at a total of 164 sites in all patients at baseline, whereas 24 sites were cured and 28 sites partially cured at Week 48. There were no aggravated or newly formed fractures/pseudofractures. At Week 96 after data cut-off, 53 sites were cured and 37 sites partially cured. There were no aggravated or newly formed fractures/pseudofractures.

In the foreign Study UX023T-CL201 in patients with TIO, its primary endpoint, namely, the percentage of patients achieving mean serum phosphorus above the lower limit of normal (2.5 mg/dL) at the midpoint[46)] of each treatment cycle between baseline and Week 24, was 52.9% (9 of 17) of patients. Burosumab administration was started at 0.3 mg/kg and the dose was increased in a stepwise manner. Serum phosphorus concentration exceeded the lower limit of normal in 82.4% of patients at Week 22, and the increased serum phosphorus level was maintained through Week 72. Osteomalacia-related histomorphological indices, another set of the primary endpoints, showed a tendency toward improvement at Week 48, except OS/BS (Table 51). In 11 patients who presented with osteomalacia at baseline, severity level decreased in all parameters shown in Table 51. Physical function and other parameters in the secondary endpoint also tended to improve.

Based on the above clinical study results, the applicant considers that burosumab is effective in patients with TIO.

PMDA's view:

Efficacy in patients with TIO should preferably be evaluated in a comparative study using placebo or conventional treatment as the control. However, it is understandable that such a comparative study is infeasible due to the limited number of patients with TIO even as compared with the number of patients with XLH. Although the cause of excess FGF23 production in TIO is different from that in XLH, both diseases are typically manifested by impaired bone mineralization caused by excess FGF production-associated hypophosphatemia. Therefore, efficacy evaluation in patients with TIO based on the results of an uncontrolled study would be inevitable. In Studies KRN23-002 and UX023T-CL201, the mean serum phosphorus concentration increased after the start of burosumab and remained above the lower limit of normal when the dose was adjusted appropriately. In addition, osteomalacia-associated tissue morphology and clinical symptoms of osteomalacia related to motor function tended to improve as well. Therefore, burosumab is effective in patient with TIO.

7.R.4 Safety

PMDA reviewed the safety of burosumab in adult and pediatric patients with XLH and in patients with TIO in Sections 7.R.4.1 to 7.R.4.3 below, based on the results of each clinical study. The safety of burosumab is acceptable provided that adverse events reported from the clinical studies are appropriately communicated to healthcare professionals. Because of the limited number of Japanese patients investigated in the clinical studies, information on the safety in burosumab therapy should be collected continuously in the post-marketing setting [see Section "7.R.8 Post-marketing investigations"]. Individual events were further reviewed in Sections 7.R.4.4 to 7.R.4.8.

7.R.4.1 Safety in adult patients with XLH

The applicant's explanation:

Table 66 shows the outline of adverse events observed in each clinical study in adult patients with XLH.

Table 66. Incidences of adverse events in clinical studies in adult patients with XLH (safety analysis population)

Event	Study UX023-CL303			Study UX023-CL304	Study KRN23-INT-001/002[a)]
	Placebo (n = 66)	Burosumab (n = 68)	All patients receiving burosumab[b)] (n = 134)	Burosumab (n = 14)	Burosumab (n = 28)
All adverse events	92.4 (61)	94.1 (64)	97.8 (131)	100 (14)	96.4 (27)
All adverse drug reactions	39.4 (26)	44.1 (30)	55.2 (74)	71.4 (10)	64.3 (18)
Serious adverse events	3.0 (2)	2.9 (2)	11.2 (15)	14.3 (2)	10.7 (3)
Serious adverse drug reactions	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Adverse events leading to treatment discontinuation	0 (0)	0 (0)	0 (0)	0 (0)	10.7 (3)
Adverse events leading to study discontinuation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Grade ≥3 adverse events	13.6 (9)	11.8 (8)	21.6 (29)	0 (0)	17.9 (5)

Incidence % (number of patients)

a) Includes patients who participated in Study KRN23-INT-001 only and patients who participated in both Studies KRN23-INT-001 and KRN23-INT-002.

b) Results in the burosumab group and the placebo group up to data cut-off after the start of burosumab administration.

During the placebo-controlled period of Study UX023-CL303, events falling under the system organ class (SOC) of "Infections and infestations" or "Musculoskeletal and connective tissue disorders" occurred frequently both in the placebo group and the burosumab group. Comparisons showed that the incidences of events falling under the SOC of "Nervous system disorders" was higher by ≥10% in the burosumab group (38.2%) than in the placebo group (24.2%). There were no events that occurred in the burosumab group at ≥10% higher incidence than in the placebo group. The event that occurred in the placebo group at ≥10% higher incidence than in the burosumab group was arthralgia (24.2% in the placebo group, 8.8% in the burosumab group) [for incidences of adverse events classified by preferred term (PT), see Table 56].

During the placebo-controlled period, serious adverse events were observed in 2 patients in the placebo group (upper respiratory tract infection and invasive ductal breast carcinoma) and in 2 patients in the burosumab group (irritable bowel syndrome and back pain). Serious adverse events were observed in 15 patients during the entire treatment period through the data cut-off, but a causal relationship to the study drug was ruled out for all events. In Study UX023-CL304, serious adverse events were observed

in 2 patients (migraine and paraesthesia), but a causal relationship to the study drug was ruled out for both events.

The Grade 3 adverse event reported in ≥2 patients in either group during the placebo-controlled period of Study UX023-CL303 was tooth abscess in 3 patients in the burosumab group. The Grade 3 adverse drug reaction was pain in extremity in 1 patient in the burosumab group. Grade 3 adverse events reported in ≥2 patients during the entire treatment period up to the data cut-off were back pain in 4 patients, arthralgia and tooth abscess in 3 patients each, and headache and muscle spasms in 2 patients each. Grade 3 adverse drug reactions observed were back pain in 2 patients, pain in extremity and renal colic in 1 patient each. In Study UX023-CL304, Grade 3 adverse events were arthralgia, paraesthesia, migraine, and uterine haemorrhage in 1 patient each, and a causal relationship to the study drug was ruled out for all events. There were no Grade 4 events either in Study UX023-CL303 or in Study UX023-CL304.

Table 67 shows the incidences of adverse events in the pooled data of Studies UX023-CL303 and UX023-CL304, classified by time to onset. There was no tendency toward increased incidence at any specific period. Comparison of the incidence of each event showed that there were events occurring frequently during the period from Weeks 0 to 11. They were back pain (Weeks 0-11, 11.5%; Weeks 12-23, 3.4%; Weeks 24-35, 2.7%; from Week 36 on, 3.7%), restless legs syndrome (Weeks 0-11, 6.8%; Weeks 12-23, 1.4%; Weeks 24-35, 1.4%; from Week 36 on, 1.9%), muscle spasms (Weeks 0-11, 7.4%; Weeks 12-23, 2.0%; Weeks 24-35, 2.0%; from Week 36 on, 1.9%), and nausea (Weeks 0-11, 7.4%; Weeks 12-23, 3.4%; Weeks 24-35, 2.7%; from Week 36 on, 0.9%).

Table 67. Incidences of adverse events by time to onset (pooled data of Studies UX023-CL303 and UX023-CL304)

	Weeks 0-11 (n = 148)	Weeks 12-23 (n = 148)	Weeks 24-35 (n = 147)	From Weeks 36 on (n = 107)
All adverse events	79.1 (117)	68.9 (102)	69.4 (102)	75.7 (81)
	1260.7 [424]	887.6 [302]	1139.6 [323]	347 [660.8]

Upper row, Incidence % (number of patients); Lower row, Number of events per 100 patient-years [number of events]

In the Japanese subpopulation of Study UX023-CL303, adverse events were observed in all of the 6 patients in the burosumab group and in 3 of 5 patients in the placebo group during the placebo-controlled period. During the entire period up to the data cut-off, adverse events were observed in all of the 11 patients. During the placebo-controlled period, adverse drug reactions were observed in 1 of 6 patients in the burosumab group and none in the placebo group. During the entire period up to the data cut-off, adverse drug reactions were observed in 4 of 11 patients (36.4%). There were no events that were serious or led to treatment discontinuation in either treatment group.

In the Japanese subpopulation of Study UX023-CL304, adverse events were observed in all of the 4 patients, and adverse drug reactions in 2 of 4 patients. There were no deaths, other serious adverse events, or adverse events leading to treatment discontinuation.

There was no specific difference in the profile of adverse events observed between the entire population and the Japanese subpopulation in the study. Also, there were no noteworthy events, such as those with higher severity, in the Japanese subpopulation.

Thus, there was no significant difference in the incidence of adverse events between the placebo group and the burosumab group in Study UX023-CL303 in adult patients with XLH. No particular safety problems were observed during the long-term treatment with burosumab in Study UX023-CL303 or Study UX023-CL304. There was no significant difference in the safety between the entire population and the Japanese subpopulation in these studies, demonstrating the safety of burosumab [for the outline of safety in burosumab administration in Studies UX023-CL303 and UX023-CL304, see Sections "7.3.1 Placebo-controlled, double-blind study in adult patients with XLH" and "7.3.2 Open-label study on the effect on osteomalacia in adult patients with XLH"].

7.R.4.2 Safety in pediatric patients with XLH

The applicant's explanation:

Table 68 shows the summary of adverse events in each clinical study on pediatric patients with XLH.

Table 68. Incidences of adverse events in clinical studies in pediatric patients with XLH (safety analysis population)

	Study UX023-CL301		Study KRN23-003		Study UX023-CL201		Study UX023-CL205
			Entire period	After the start of self-injection			
	Burosumab (n = 29)	Control (n = 32)	Burosumab (n = 15)	Burosumab (n =15)	Q2W (n = 26)	Q4W (n = 26)	Q2W (n = 13)
All adverse events	100 (29)	84.4 (27)	93.3 (14)	80.0 (12)	100 (26)	100 (26)	100 (13)
All adverse drug reactions	58.6 (17)	21.9 (7)	13.3 (2)	6.7 (1)	65.4 (17)	73.1 (19)	38.5 (5)
Serious adverse events	10.3 (3)	9.4 (3)	6.7 (1)	6.7 (1)	0 (0)	3.8 (1)	7.7 (1)
Serious adverse drug reactions	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3.8 (1)	0 (0)
Adverse events leading to treatment discontinuation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Adverse events leading to study discontinuation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Grade ≥3 adverse events	13.8 (4)	9.4 (3)	6.7 (1)	6.7 (1)	3.8 (1)	3.8 (1)	7.7 (1)

Incidence % (number of patients)

In Study UX023-CL301 in pediatric patients aged 1 to 12 years with XLH, either the adverse events occurred or their severity in the burosumab group were not particularly problematic. The incidence of adverse events tended to be higher in the burosumab group than in the control group receiving oral phosphate and active vitamin D_3. Events (SOC) with a higher incidence in the burosumab group were "General disorders and administration site conditions," which suggested that the observed difference was due to the different route of administration of each drug (subcutaneous vs. oral). The most commonly reported event in the burosumab group was pyrexia, which was Grade 1 or 2 and of no clinical significance [see Table 62 for the incidences of adverse events classified by PT]. Serious adverse events were observed in 3 patients in the burosumab group (craniosynostosis, viral infection, and migraine) and in 3 patients in the control group (haematuria, craniosynostosis, and knee deformity), and a causal relationship to the study drug was ruled out for all events. Grade 3 adverse events were observed in 4 patients in the burosumab group (arthralgia, dysuria, gastroenteritis viral, and urine ketone body present) and in 3 patients in the control group (arthralgia, food allergy, and craniosynostosis). Only

arthralgia in the burosumab group was assessed as an adverse drug reaction. No Grade 4 adverse events were observed. Among Japanese patients enrolled in Study UX023-CL301, adverse events occurred in 2 of 2 patients in the burosumab group and in 1 of 3 patients in the placebo group. Adverse drug reactions and serious adverse events were not observed in either group.

In Study KRN23-003 in Japanese pediatric patients aged 1 to 12 years with XLH, the safety profile was not significantly different from that in Study UX023-CL301. There were no noteworthy adverse events after the start of self-injection, suggesting that self-infection of burosumab could be performed without any particular problem.

In Study UX023-CL205 in pediatric patients aged 1 to 4 years with XLH and in Study UX023-CL201 investigating Q2W and Q4W dosage regimens in pediatric patients aged 5 to 12 years with XLH as well, no particular problems were observed in the incidences of adverse events. Table 69 shows the incidences of adverse events classified by time to onset in Studies UX023-CL301 and KRN23-003. There was no tendency toward increased incidence during any particular period. Comparison of individual events showed, in Study UX023-CL301, events that occurred with a higher incidence during Weeks 0 to 11 or from Week 36 on. The event with a higher incidence during Weeks 0 to 11 was injection site reaction (Weeks 0-11, 13.8%; Weeks 12-23, 3.4%; Weeks 24-35, 3.4%; from Week 36 on, 3.4%), and events with a higher incidence from Week 36 on were arthralgia (Weeks 0-11, 13.8%; Weeks 12-23, 6.9%; Weeks 24-35, 20.7%; from Week 36 on, 34.5%), dental caries (Weeks 0-11, 6.9%; Weeks 12-23, 6.9%; Weeks 24-35, 3.4%; from Week 36 on, 17.2%), fall (Weeks 0-11, 0%; Weeks 12-23, 0%; Weeks 24-35, 0%; from Week 36 on, 10.3%), and vitamin D decreased (Weeks 0-11, 3.4%; Weeks 12-23, 3.4%; Weeks 24-35, 0%; from Week 36 on, 13.8%). Since adverse events from Week 36 include events occurring during the 28-week period from Weeks 36 to 64, the above results suggest that there is no clear tendency toward increased risks of these events after Week 36. In Study KRN23-003, there were no events that occurred at a higher incidence during a specific period than other periods.

Table 69. Incidences of adverse events by time to onset
(Studies UX023-CL301 and KRN23-003, safety analysis population)

	Study UX023-CL301[a)]				Study KRN23-003[b)]			
	Weeks 0-11	Weeks 12-23	Weeks 24-35	From Week 36 on	Weeks 0-11	Weeks 12-23	Weeks 24-35	From Week 36 on
All adverse events	93.1 (27)	86.2 (25)	89.7 (26)	96.6 (28)	53.3 (8)	60.0 (9)	46.7 (7)	13.3 (2)
	2003.0 [132]	1589.3 [106]	1634.3 [109]	981.1 [215]	322.7 [11]	492.8 [17]	260.9 [9]	404.0 [5]

Upper row, Incidence % (number of patients); Lower row, Number of events per 100 patient-years [number of events]
a) n = 29, b) n = 15

The above results show that there were no particular clinical problems in the safety profiles observed in each clinical study in pediatric patients with XLH. In Study UX023-CL301, there was no significant difference in safety between the entire population and the Japanese subpopulation. Results of Study KRN23-003 in Japanese patients also confirmed the safety of burosumab [for the outline of safety of burosumab in each clinical study, see Sections “7.3.3 Open-label comparative study in pediatric patients with XLH” and “7.3.4 Open-label study in Japanese pediatric patients with XLH,” etc.].

7.R.4.3 Safety in patients with TIO

The applicant's explanation:

Table 70 shows the incidences of adverse events in clinical studies in patients with TIO.

Table 70. Incidences of adverse events in clinical studies in patients with TIO (safety analysis population)

	Study KRN23-002	Study UX023T-CL201
	Burosumab (n = 13)	Burosumab (n = 17)
All adverse events	92.3 (12)	100 (17)
All adverse drug reactions	38.5 (5)	41.2 (7)
Serious adverse events	23.1 (3)	35.3 (6)
Serious adverse drug reactions	0 (0)	0 (0)
Death	0 (0)	5.9 (1)
Adverse events leading to treatment discontinuation	0 (0)	5.9 (1)
Adverse events leading to study discontinuation	0 (0)	0 (0)
Grade ≥3 adverse events	23.1 (3)	47.1 (8)

Incidence % (number of patients)

In Study KRN23-002 in Japanese and Korean patients with TIO, adverse drug reactions were observed in 5 patients, all of which were Grade 1 or 2. No death occurred. Serious adverse events were observed in 3 patients (septic shock/gastroenteritis, septic shock, and herpes zoster), and a causal relationship to the study drug was ruled out for all events. Four Japanese patients self-injected the study drug. Adverse events that occurred after self-injection were nasopharyngitis in 3 patients and influenza, proctitis, contusion, and tooth fracture in 1 patient each. There were no adverse drug reactions, nor were any events of particular concern.

Table 71 shows the incidences of adverse events classified by the time to onset in Study KRN23-002. There was no tendency of an increase in the incidence of either any event or all events combined during any specific period.

Table 71. Incidences of adverse events by time to onset (Study KRN23-002, safety analysis population)

	Weeks 0-11 (n = 13)	Weeks 12-23 (n = 13)	Weeks 24-35 (n = 12)	From Week 36 on (n = 12)
All adverse events	61.5 (8)	53.8 (7)	50.0 (6)	91.7 (11)
	744.7 [22]	533.0 [15]	362.4 [10]	490.0 [59]

Upper row, Incidence % (number of patients); Lower row, Number of events per 100 patient-years [number of events]

In Study UX023T-CL201 in non-Japanese patients with TIO, death was reported in 1 patient, who presented with cardiac arrest. This patient had gallstone pancreatitis and underwent endoscopic retrograde cholangiopancreatography with endoscopic sphincterotomy and balloon extraction. After the operation, the patient experienced acute respiratory failure and septic shock, and died of cardiac arrest. A causal relationship of the death to the study drug was ruled out. Serious adverse events were observed in 6 patients, which included neoplasm progression in 4 patients. There were no other serious events reported in ≥2 patients. A causal relationship to the study drug was ruled out for all events.

These results suggest no specific concerns about the safety profiles in any of the clinical studies conducted in patients with TIO [for the outline of safety of burosumab in Studies KRN23-002 and UX023T-CL201, see Sections "7.2.3 Phase II open-label study in patients with TIO or ENS" and "7.2.4 Phase II open-label study in non-Japanese patients with TIO or ENS"].

7.R.4.4 Hypersensitivity

The applicant's explanation:

In Study UX023-CL303, one of the clinical studies in adult patients with XLH, the incidence of adverse events related to hypersensitivity[47)] during the placebo-controlled period was 6.1% (4 of 66) in the placebo group and 5.9% (4 of 68) in the burosumab group, showing similar results between the 2 groups. Observed events were rash in 3 patients and urticaria in 1 patient in the placebo group; and dermatitis contact, injection site rash, eczema, and urticaria contact in 1 patient each in the burosumab group. Injection site rash in 1 patient of the burosumab group was assessed as an adverse drug reaction. Among all patients receiving the study drug, the incidence of hypersensitivity-related adverse events up to the data cut-off was 11.2% (15 of 134). Hypersensitivity-related adverse events reported in ≥2 patients were rash in 3 patients and dermatitis contact, urticaria, and injection site hypersensitivity in 2 patients each. Injection site hypersensitivity in 2 patients, injection site urticaria, injection site rash, and rash in 1 patient each were assessed as adverse drug reactions. All hypersensitivity-related events that occurred during the placebo-controlled period or up to data cut-off were Grade 1 or 2. In Study UX023-CL304, hypersensitivity-related adverse events were observed in 57.1% (8 of 14) of patients. Events reported in ≥2 patients were injection site urticaria in 3 patients and rash, drug hypersensitivity, and gingival swelling in 2 patients each. All events were Grade 1 or 2 in severity, and adverse drug reactions were injection site urticaria in 3 patients and rash and urticaria in 1 patient each.

In Study UX023-CL301 in pediatric patients with XLH, the incidence of hypersensitivity-related adverse events was 37.9% (11 of 29) in the burosumab group and 18.8% (6 of 32) in the control group. Adverse events reported in ≥2 patients in either group were injection site rash and rash in 3 patients each and injection site urticaria and rhinitis allergic in 2 patients each in the burosumab group; and rash and hypersensitivity in 2 patients each in the control group. All events were Grade 1 or 2. Injection site rash in 3 patients, injection site urticaria in 2 patients, and injection site hypersensitivity, rash generalized, and injection related reaction in 1 patient each were assessed as adverse drug reactions. In Study KRN23-003, the incidence of hypersensitivity-related events was 13.3% (2 of 15). Events observed were rash and urticaria in 1 patient each. These events were Grade 1 in severity, and a causal relationship to the study drug was ruled out. All of them were observed after self-injection was started.

In Study KRN23-002, one of the clinical studies in patients with TIO, the incidence of hypersensitivity-related events was 23.1% (3 of 13). Events observed were eczema and rash in 2 patients each and drug eruption and injection site hypersensitivity in 1 patient each. Of these, rash and injection site hypersensitivity in 1 patient each were assessed as adverse drug reactions. All events were Grade 1 or 2 in severity. In Study UX023T-CL201, another clinical study in patients with TIO, the incidence of hypersensitivity-related events was 11.8% (2 of 17). Events observed were application site rash and rash in 1 patient each, and the rash in 1 patient was assessed as adverse drug reaction. Both events were Grade 1 in severity.

In Study KRN23-INT-001, 1 patient with injection site urticaria discontinued study drug administration. This patient had the adverse event on the day of the third dose of burosumab, which resolved after

47) Preferred terms classified in "Hypersensitivity (narrow)" in Standardised MedDRA queries (SMQ)

burosumab discontinuation and medication. The event was Grade 2 in severity and assessed as an adverse drug reaction. No anaphylactic signs such as wheezing were observed.

The above clinical study results showed that the incidence of hypersensitivity-related adverse events did not significantly differ between after placebo administration and after burosumab administration. There were no Grade ≥3 events. The only hypersensitivity-related event leading to treatment discontinuation was injection site urticaria in 1 patient in Study KRN23-INT-001. The event resolved after burosumab discontinuation and medication, and no anaphylactic signs were observed. However, because of a possible risk of serious hypersensitivity reaction that cannot be excluded, and attention will be called to hypersensitivity-related events via the package insert, and these events will be subject to further monitoring in the post-marketing setting.

PMDA's view:
No serious hypersensitivity such as anaphylaxis was observed in clinical studies. In addition, the incidence of hypersensitivity-related events was similar between the placebo group and the burosumab group in the placebo-controlled Study UX023-CL303 in adult patients with XLH. Given these, the hypersensitivity-related risk of burosumab is acceptable. As proposed by the applicant, the package insert should highlight the occurrence, etc. of hypersensitivity-related events observed in the clinical studies.

7.R.4.5 Hyperphosphatemia-related events

The applicant's explanation:
Burosumab binds to FGF23 and neutralizes FGF23 activity which leads to increased serum phosphorus concentration. That is to say, the pharmacological action of burosumab may induce hyperphosphatemia. Hyperphosphatemia-related events were therefore investigated. During the placebo-controlled period of Study UX023-CL303 in adult patients with XLH, the incidence of hyperphosphatemia-related adverse events (the PT of "hyperphosphataemia" or "blood phosphorus increased" in Medical dictionary for regulatory activities [MedDRA]) was 0% (0 of 66) in the placebo group and 5.9% (4 of 68) in the burosumab group. The incidence during the entire treatment period up to data cut-off was 6.0% (8 of 134). All of the events were assessed as adverse drug reactions but were Grade 1 or 2 in severity. In Study UX023-CL304, no hyperphosphatemia-related adverse events were observed. In Studies UX023-CL301 and KRN23-003 in pediatric patients with XLH and in Study KRN23-002 in patients with TIO, no hyperphosphatemia-related adverse events were observed. In Study UX023T-CL201 in patients with TIO, hyperphosphatemia-related adverse events were observed in 2 patients (11.8%), which were assessed as Grade 1 adverse drug reactions.

Serum phosphorus concentration of ≥6.5 mg/dL was not observed in any of the patients in clinical studies. In Study UX023-CL303 in adult patients with XLH, serum phosphorus concentration exceeded the upper limit of normal at least once during the placebo-controlled period in 9 patients (13.2%) in the burosumab group. Of these, 5 patients required dose reduction, after which serum phosphorus concentration rapidly decreased within the normal range. In the placebo group, there were no patients showing serum phosphorus concentration exceeding the upper limit of normal. During the treatment continuation period, serum phosphorus concentration increased above the upper limit of normal in 8

patients (12.1%) in the placebo/burosumab group. Of these, 4 patients required burosumab dose reduction, after which serum phosphorus concentration rapidly decreased within the normal range. In Study UX023-CL304, serum phosphorus concentration did not increase above the upper limit of normal. In Studies UX023-CL301 and KRN23-003 in pediatric patients with XLH, serum phosphorus concentration did not increase above the upper limit of normal in any of the patients.

The above clinical study results showed that hyperphosphatemia-related adverse events were observed after burosumab administration, none of them, however, were of high severity. Further, although serum phosphorus concentration exceeded the upper limit of normal in some patients, the concentration was controllable by dose reduction. These results suggest that the risk of hyperphosphatemia-related adverse events can be controlled within the acceptable level by early detection of increased serum phosphorus concentration and appropriate measures such as dose reduction. Accordingly, healthcare professional will be advised via the package insert to monitor serum phosphorus concentration regularly.

PMDA's view:
Hyperphosphatemia-related events observed after burosumab administration in the clinical studies were not severe and were controllable by dose adjustment. Therefore, the risk of hyperphosphatemia-related events is acceptable when burosumab is used with appropriate advice on regular measurement of serum phosphorus concentration, etc.

7.R.4.6 Heterotopic calcification-related events

The applicant's explanation:
In Study UX023-CL303, one of the studies in adult patients with XLH, heterotopic calcification-related adverse events[48)] were not observed during the placebo-controlled period, but observed in 9 patients (6.7%) during the entire period up to the data cut-off. Events observed were nephrocalcinosis in 6 patients and nephrolithiasis in 3 patients. All events were Grade 1 or 2 in severity. These events, except for nephrolithiasis in 2 patients, were adverse drug reactions. No heterotopic calcification-related events were observed in Study UX023-CL304, another study in adult patients with XLH, or in Studies UX023-CL301 and KRN23-003 in pediatric patients with XLH and in Study KRN23-002 in patients with TIO. In Study UX023T-CL201 in non-Japanese patients with TIO, heterotopic calcification-related adverse events[49)] were observed in 2 patients (11.8%). The events observed were calculus bladder and nephrolithiasis in 1 patient each, both of which were Grade 1 or 2 in severity. A causal relationship to the study drug was ruled out for all events.

Kidney calcification was assessed by ultrasonography according to the 5-grade scale from 0 (normal) to 4 (calculus). During the placebo-controlled period of Study UX023-CL303 in adult patients with XLH, baseline score was 0 in 50.0% (34 of 68) of patients in the burosumab group and 40.9% (27 of 66) of patients in the placebo group, and score 0 was maintained up to Week 24 in 33.8% (23 of 68) of patients in the burosumab group and in 27.3% (18 of 66) of patients in the placebo group. Baseline score was 1 (faint echo signal at the border of the renal pyramid) in 33.8% (23 of 68) of patients in the burosumab group and in 48.5% (32 of 66) of patients in the placebo group, and this score was maintained in 26.5%

48) Events were counted based on the applicant's definition of heterotopic calcification-related events.
49) MedDRA PTs containing the term "calcification" were counted.

(18 of 68) of patients in the burosumab group and in 39.4% (26 of 66) of patients in the placebo group. In Study UX023-CL304, baseline score was 0 in 42.9% (6 of 14) of patients, and this score was maintained up to Week 48 in 35.7% (5 of 14) of patients. Baseline score was 1 in 50.0% (7 of 14) of patients, and this score was maintained in 42.9% (6 of 14) of patients. In Studies UX023-CL303 and UX023-CL304, there were no patients who showed a change in score by ≥2 levels. Cardiac calcification was evaluated by ultrasonography according to a 9-grade scale from Grade 0 (no finding) to Grade 8 (extensive calcification). During the placebo-controlled period of Study UX023-CL303 in adult patients with XLH, baseline score was Grade 0 in 88.2% (60 of 68) of patients in the burosumab group and 89.4% (59 of 66) of patients in the control group, and score of Grade 0 was maintained up to Week 24 in 82.4% (56 of 68) of patients in the burosumab group and in 75.8% (50 of 66) of patients in the placebo group. In Study UX023-CL304, baseline score was Grade 0 in 92.9% of patients, and this score was maintained in all patients up to Week 48. In Studies UX023-CL303 and UX023-CL304, there were no patients who showed a change in Grade by ≥2 levels. In Study UX023-CL301 in pediatric patients with XLH, there were no patients who showed heterotopic calcification at any time point. In Study KRN23-003, kidney calcification was evaluated by ultrasonography according to the above 5-grade rating scale. As a result, baseline score was 0 in all of the 15 patients, and this score was maintained up to Week 40 in 13 patients. There were no patients who showed a change in score by ≥2 levels. There were no patients who showed an abnormality on ultrasonography of heart or kidney. In Study KRN23-002 in patients with TIO, scoring assessment was not performed, but kidney calcification not detected before burosumab administration was newly observed in 1 patient by the test at the study discontinuation. This patient, who discontinued the study because of aggravation of the primary disease, showed no decrease in estimated glomerular filtration rate (eGFR), suggesting no effect on the kidney. Cardiac ultrasonography showed that there were no patients who had newly formed calcification after the start of administration. In Study UX023T-CL201, no clinically significant change was detected in kidney calcification score by kidney ultrasonography or in heterotopic calcification of heart by cardiac ultrasonography.

Thus, the above clinical study results showed that there were only few heterotopic calcification-related adverse events and that no clinically significant change related to heterotopic calcification was detected by ultrasonography, suggesting that burosumab is unlikely to cause heterotopic calcification. However, taking account of the fact that heterotopic calcification, once manifest, is clinically significant and that heterotopic calcification is reported in patients treated with the conventional therapy with oral phosphate and active vitamin D_3 (*J Bone Miner Res.* 2011;26:1381-8), the importance of the use of imaging test and intact PTH measurement as necessary will be communicated to healthcare professionals via the package insert.

PMDA accepted the applicant's explanation.

7.R.4.7 Restless legs syndrome

The applicant's explanation:

Restless legs syndrome is related to various chronic conditions including genetic factors, diabetes mellitus, renal failure, thyroid disease, and electrolyte imbalance, as well as chronic hyperphosphatemia in patients on dialysis. Restless legs syndrome was observed in 18.5% (5 of 27) of adult patients with

XLH in Study KRN23-INT-001, which was conducted in the early stage of burosumab development, and 14.3% (3 of 21) of patients in Study KRN23-INT-002. Because 1 patient in Study KRN23-INT-002 experienced Grade 3 restless legs syndrome and discontinued the study, "restless legs syndrome" was evaluated as a notable risk in subsequent studies.

During the placebo-controlled period of Study UX023-CL303 in adult patients with XLH, restless legs syndrome-related adverse events were observed in 4 patients (6.1%) in the placebo group and 8 patients (11.8%) in the burosumab group. All observed events were assessed as adverse drug reactions. Restless legs syndrome-related adverse events were observed in 15 patients through the entire period up to the data cut-off, and all of them except for the event in 1 patient were adverse drug reactions of Grade 1 or 2. In Study UX023-CL304, restless legs syndrome-related adverse event was observed in 1 patient and assessed as an adverse drug reaction of Grade 2. In Studies UX023-CL301 and KRN23-003 in pediatric patients with XLH, no restless legs syndrome-related events were observed. In terms of patients with TIO, restless legs syndrome-related adverse events were not observed in Study KRN23-002, but observed in 2 patients (11.8%) in Study UX023T-CL201. None of the restless legs syndrome-related adverse events observed in Studies UX023-CL303, UX023-CL304, and UX023T-CL201 led to treatment discontinuation.

As shown, restless legs syndrome-related adverse events were observed in a certain percentage in the clinical studies in adult patients. However, the incidence observed during the placebo-controlled period of Study UX023-CL303 did not significantly differ between the placebo group and the burosumab group, and the event was not considered specific to burosumab. In addition, all observed events were Grade 1 or 2, and some patients experiencing restless legs syndrome-related events had a family history of restless legs syndrome.

The above results suggest that restless legs syndrome-related events observed after burosumab therapy are of little clinical significance. Therefore, these events are not notable risks with burosumab. Nevertheless, since a certain number of adult patients with XLH had restless legs syndrome-like symptoms, “Lower extremities discomfort” will be included in the “Other adverse drug reactions” section of the package insert as a precaution, based on the events reported in clinical studies.

PMDA’s view:
During the placebo-controlled period of Study UX023-CL303 in adult patients with XLH, the incidence of restless legs syndrome-related events tended to be higher in the burosumab group than in the placebo group. However, only 1 patient in Study KRN23-INT-002 experienced an event leading to treatment discontinuation and other events were non-severe. Therefore, currently restless legs syndrome-related events are unlikely to pose a clinically significant problem in burosumab therapy and the measures proposed by the applicant are acceptable.

7.R.5 Indication

The applicant’s explanation:
Calcium and phosphate, the main components of hydroxyapatite, are essential for the growth and calcification of bones, and insufficiency of either of them is a cause of increased osteoids due to

inhibition of bone and cartilage calcification, leading to decreased bone strength. Increased osteoids lead to development of rickets before the closure of growth cartilage, and osteomalacia after the closure. Rickets and osteomalacia caused by decreased serum phosphorus concentration due to excess FGF23 production (serum FGF23 concentration ≥30 pg/mL) are defined as FGF23-related hypophosphatemic rickets/osteomalacia (*The Japanese journal of endocrinology*. 2015;91(suppl):1-11).

FGF23-related hypophosphatemic rickets/osteomalacia are rare diseases. According to a survey of the Japanese Society for Pediatric Endocrinology, there are 135 patients with persistent hypophosphatemia in Japan, and of these, 126 patients had hereditary hypophosphatemia (*Clin Pediatr Endocrinol.* 2013;22:9-14). According to a survey of a study group on abnormalities in the hormone receptor mechanism, the number of patients with FGF23-related hypophosphatemic diseases was 311 during the 5-year period from 2005 to 2009, and additional 63 patients were reported in 2009. Among 84 patients who responded to the secondary survey, 41 patients had hereditary hypophosphatemic disease and 35 patients had TIO. Of those reported to have hereditary hypophosphatemic disease, 36 patients had XLH (*Endocr J*. 2015;62:811-6).

The results of comparison with the placebo group in Study UX023-CL303 in adult patients with XLH, comparison with the control group (treated with oral phosphate and active vitamin D_3) in Study UX023-CL301 in pediatric patients with XLH, and Study KRN23-002 in patients with TIO, etc., demonstrated the efficacy of burosumab with acceptable safety in adult and pediatric patients with XLH and in patients with TIO.

Besides XLH and TIO, FGF23-related hypophosphatemic rickets/osteomalacia, diseases include germ cell mutation-induced hereditary diseases as with XLH (autosomal dominant hypophosphatemic rickets/osteomalacia [ADHR], autosomal recessive hypophosphataemic rickets/osteomalacia 1, 2 [ARHR1, 2], Raine syndrome, Jansen's metaphyseal dysostosis, and osteoglophonic dysplasia [OD]), somatic cell mutation-induced diseases (McCune-Albright syndrome [MAS]/fibrous dysplasia [FD] cutaneous skeletal hypophosphataemia syndrome [CSHS]/epidermal naevus syndrome [ENS]), and acquired FGF23-related hypophosphatemia that develops after the administration of saccharated iron oxide or iron polymaltose. Except in TIO and acquired FGF23-related hypophosphatemia following the administration of saccharated iron oxide or iron polymaltose, genetic mutations[50)] are the causes of the diseases as with XLH, and excess FGF production leads to hypophosphatemia and to decreased TmP/GFR. Serum $1,25(OH)_2D$ concentration can decrease to below the normal range, while serum calcium and PTH concentrations generally remain within the normal range. These biochemical findings are similar to those observed with XLH and TIO. Germ cell mutation-induced diseases are hereditary and usually develop from childhood. MAS/FD and CSHS/ENS caused by somatic cell mutation also develop from childhood as with hereditary diseases because gene mutation is established during the fetal stage. Diseases other than FGF23-related hypophosphatemia caused by the administration of saccharated iron oxide or iron polymaltose are treated with oral phosphate and active vitamin D_3 as with XLH. Like patients with XLH or TIO, these patients show the following clinical symptoms caused by decreased serum phosphorus concentration and impaired mineralization of bones: curved long bones

[50)] Responsible genes: *PHEX* in XLH, *FGF23* in ADHR, *DMP1* and *ENPP1* in ARHR1, 2, *FAM20C* in Raine syndrome, *PTHR1* in Jansen's metaphyseal dysostosis, *FGFR1* in OD, GANS in MAS and FD, and *HRAS*, *NRAS*, and *KRAS* in CSHS and ENS.

such as knock-knees and bow-legs and growth disorder in childhood, and fractures or pseudofractures and accompanying bone pain and pain associated with enthesopathy in adulthood after the closure of growth plate. Thus, diseases categorized into FGF23-related hypophosphatemic rickets/osteomalacia which were not investigated in the clinical studies are expected to present with clinical signs and symptoms similar to those observed in patients with XLH or TIO.

There is only scanty evidence on the effect of long-term conventional therapies such as oral phosphate and active vitamin D_3 on final height or on pain or motor function of adult patients with diseases other than XLH and TIO. However, in light of the observation that clinical symptoms and other findings are very similar among different types of FGF23-related hypophosphatemic rickets/osteomalacia, burosumab is expected to be also effective for diseases other than XLH and TIO. Therefore, burosumab is useful for a variety of diseases classified to FGF23-related hypophosphatemic rickets/osteomalacia. The only exception is FGF23-related hypophosphatemia induced by the administration of saccharated iron oxide or iron polymaltose. Since discontinuing these drugs rapidly leads to a decrease in blood FGF23 concentration and an increase in serum phosphorus concentration, these patients are not subjected to burosumab therapy.

Based on the above, the indication of burosumab is proposed as "FGF23-related hypophosphatemic rickets/osteomalacia."

PMDA's view:
The clinical studies demonstrated the efficacy of burosumab in patients with XLH and TIO [see Section "7.R.3 Efficacy"] with an acceptable safety profile [see Section "7.R.4 Safety"]. Thus the proposed indication of burosumab, "FGF23-related hypophosphatemic rickets/osteomalacia," is reasonable. Also, burosumab is expected to show a certain level of efficacy in non-XLH or non-TIO diseases that were not investigated in the clinical studies, because they are primarily characterized by impaired mineralization of bones due to decreased serum phosphorus concentration caused by excess FGF23 production, and burosumab has the pharmacological effect of neutralizing excess FGF23. Also, the limited number of patients with non-XLH or non-TIO diseases, even as compared with the number of patients with XLH or TIO, preclude the clinical studies. Given these, the proposed indication of burosumab, "FGF23-related hypophosphatemic rickets/osteomalacia," is appropriate. There is no available information on the safety or efficacy of burosumab in patients with non-XLH or non-TIO, and the safety and efficacy of burosumab in these patients should be verified in the post-marketing setting [see Section "7.R.8 Post-marketing investigations"]. Burosumab is not indicated for FGF23-related hypophosphatemia that occurs after the administration of saccharated iron oxide or iron polymaltose, and this should be highlighted in the package insert.

7.R.6 Dosage and administration

7.R.6.1 Dosage and administration in patients with XLH

7.R.6.1.1 Dosage and administration in adult patients with XLH

The applicant's explanation:
In Study KRN23-INT-001 in adult patients with XLH, serum phosphorus concentration increased with escalated dose of burosumab administered subcutaneously once every 4 weeks (Table 39). In Study

KRN23-INT-002, a treatment continuation study of Study KRN23-INT-001, the initial dose of burosumab (mean ± SD) was 0.54 ± 0.20 mg/kg, which was specified to be the same as the last dose in Study KRN23-INT-001. In Study KRN23-INT-002, the mean dose at the fourth to 12th administration ranged from 0.81 to 0.88 mg/kg, with 60% to 74% of patients receiving 1 mg/kg. The results showed that serum phosphorus concentration was maintained at an elevated level during most of each treatment cycle and did not increase above 4.5 mg/dL, the upper limit of normal, in any patient throughout the treatment period.

Based on the results of these clinical studies, the starting dosage regimen in the global phase III studies (Studies UX023-CL303 and UX023-CL304) in adult patients with XLH was 1 mg/kg Q4W (the dose for each patient was calculated from the baseline body weight and rounded to the nearest 10 mg, with the maximum dose of 90 mg). If serum phosphorus concentration exceeded 5.0 mg/dL even once, the dose was halved. If serum phosphorus concentration was >4.5 mg/dL and ≤5.0 mg/dL, the dose was halved only when serum phosphorus concentration exceeded >4.5 mg/dL again.

In Study UX023-CL303, the percentage of patients achieving mean serum phosphorus above the lower limit of normal (2.5 mg/dL) at the midpoint of each treatment cycle between baseline and Week 24, the primary efficacy endpoint, was significantly higher in the burosumab group (94.1%) than in the placebo group (7.6%). During the placebo-controlled period (24 weeks after the start of administration), serum phosphorus concentration exceeded the upper limit of normal of 4.5 mg/dL in 9 patients (13.2%) in the burosumab group, and the dose of burosumab was halved in 5 patients. In 4 of the 5 patients, serum phosphorus concentration was maintained within the normal range and, in the remaining 1 patient, serum phosphorus concentration was maintained within the normal range after further reduction of the dose to 0.2 mg/kg. No serious adverse events were observed in any of the 9 patients with serum phosphorus concentration exceeding the upper limit of normal, and treatment discontinuation occurred only in 1 patient who withdrew consent.

In Study UX023-CL304, burosumab improved osteomalacia-related histomorphological indices. The percentage of patients achieving mean serum phosphorus above the lower limit of normal (2.5 mg/dL) at the midpoint of each treatment cycle between baseline and Week 24 was 92.9% (13 of 14) of patients. There were no patients with serum phosphorus concentration exceeding the upper limit of normal.

Based on the above, the applicant considers that the following dosage regimen is appropriate for adult patients with XLH: The treatment is started with the dosage regimen of burosumab 1 mg/kg Q4W (the dose for each patient is calculated from the baseline body weight and rounded to the nearest 10 mg, with the maximum dose being 90 mg), and the dose is decreased appropriately depending on the serum phosphorus concentration, symptoms, etc.

7.R.6.1.2 Dosage regimen in pediatric patients with XLH

The applicant's explanation:

Children need phosphorus for the growth of bones and have faster metabolic turnover of bones than adults, and the standard serum phosphorus concentrations in children are higher (at age12, 3.6-5.8 mg/dL) than in adults. Therefore, in Study UX023-CL201 in pediatric patients with XLH, Q2W

regimens was investigated in addition to Q4W regimens investigated in adult patients with XLH, to maintain stable serum phosphorus concentration. The starting dose was 0.2, 0.4, or 0.6 mg/kg in the Q4W group and 0.1, 0.2, or 0.3 mg/kg in the Q2W group. The dose was adjusted every 4 weeks. Based on serum phosphorus concentration at Week 2, the dose could be increased by 0.3 mg/kg at a time in the Q2W group and by 0.4 mg/kg at a time in the Q4W group up to 2 mg/kg, and the maximum dose was 90 mg. The results showed that serum phosphorus concentration in the Q2W group varied less than in the Q4W group, and increased more steadily (Figure 1). Also, growth-related indices showed better improvement in the Q2W group than in the Q4W group. The incidence of adverse events did not significantly differ between the two groups. The dose of burosumab in the Q2W group was around 0.8 mg/kg at Week 24 and around 1 mg/kg at Week 40 to 64 (Table 43).

Based on the above results, the global phase III study (Study UX023-CL301) was started with the dosage regimen of 0.8 mg/kg Q2W. In patients who failed to show a sufficient increase in serum phosphorus concentration, the dose could be increased to 1.2 mg/kg, with the maximum dose of 90 mg.

A significant improvement was observed in the RGI-C global score at Week 40, the primary endpoint, in the burosumab group compared with the control group. In the burosumab group, serum phosphorus concentration increased after the start of administration, and the mean concentration exceeded 3.2 mg/dL, the lower limit of normal, at almost all measuring time points up to Week 40. In contrast, the mean concentration in the control group did not exceed the lower limit of normal (Table 43). In the Japanese Study KRN23-003 conducted using the same dosage regimen as that in Study UX023-CL301, serum phosphorus concentration increased from baseline after the start of administration, reached the peak level at Week 4, and the increased level was maintained without significant variations up to Week 40. In Studies UX023-CL301 and KRN23-003, serum phosphorus concentration did not exceed 6.1 mg/dL, the upper limit of normal, in any of the patients.

Based on the above, the applicant considers that the following dosage regimen is appropriate for pediatric patients with XLH: The treatment is started with the dosage regimen of burosumab 0.8 mg/kg Q2W, and the dose is adjusted appropriately depending on the serum phosphorus concentration, symptoms, etc. The maximum dose should be 2 mg/kg (90 mg at the maximum), taking account of the following observations: (1) In Study UX023-CL201 with the maximum dose of 2 mg/kg (90 mg at the maximum) in both Q2W and Q4W groups, an adverse event of "serum phosphorus increased" occurred in 1 patient, but actual serum phosphorus concentration was within the normal range and the serum phosphorus concentration did not exceed the upper limit of normal in any patients at any measuring time point; and (2) no hyperphosphatemia-related events or heterotopic calcification-related events occurred during treatment with 2 mg/kg in 8 patients in whom the dose was increased to 2 mg/kg, and serious adverse events "pyrexia" and "myalgia" observed in 1 patient resolved without change in the dose of burosumab.

The clinical studies in pediatric patients with XLH enrolled patients aged ≤12 years, and the clinical studies in adult patients with XLH enrolled patients aged ≥18 years. Therefore, efficacy and safety in patients aged 13 to 17 years with XLH have not been investigated. However, in each clinical study in pediatric patients aged 1 to 12 years with XLH and adult patients with XLH, the efficacy of burosumab

was confirmed in patients before and after the closure of growth cartilage with an acceptable safety profile. Therefore, the applicant considers that, even in the patient group 13 to 17 years of age including patients with differing extent of growth cartilage closure, burosumab is expected to be safe and effective on the premise that the dose of burosumab is adjusted according to the serum phosphorus concentration, as practiced in pediatric patients aged 1 to 12 years with XLH and adult patients with XLH. Using the serum burosumab concentration and serum phosphorus concentration data obtained from clinical studies, a population pharmacokinetics model [see Section "6.2.4.1 Population pharmacokinetic analysis in patients with XLH"] and a population pharmacokinetic/pharmacodynamic model[51] were constructed. The models were used to estimate serum burosumab concentration and serum phosphorus concentration under the steady state following the administration of burosumab to adolescent patients aged 12 to 17 years with XLH using the dosage regimens for pediatric patients with XLH (0.8 mg/kg Q2W) and for adult patients with XLH (1 mg/kg Q4W).[52] The following values were estimated in subcutaneous burosumab 0.8 mg/kg Q2W and 1 mg/kg Q4W: Peak serum phosphorus concentration under a steady state (median value), 3.34 and 3.30 mg/dL, respectively; the lowest concentration, 3.18 and 2.93 mg/dL, respectively, and the percentage of patients with peak serum concentration of >5.0 mg/dL, 2.9% and 3.3%, respectively. These results suggested that, in patients aged 13 to 17 years with XLH, the subcutaneous administration of burosumab is expected to increase serum phosphorus concentration to a certain extent, regardless of either 0.8 mg/kg Q2W or 1 mg/kg Q4W.

The goal of XLH treatment differs between children and adults. In children, XLH is treated to improve growth disorder, bone deformity, and motor dysfunction, whereas in adults, the chief purposes are to alleviate pain, improve osteomalacia and motor dysfunction, and cure fracture. In patients with XLH in transition from children to adults, whether to change the therapeutic goal is judged based on the bone age, a parameter commonly used as an index for the growth status. In patients who have not reached the adult bone age (approximately 17 years in boys and 15 years in girls), the same treatment as that given to children are required. It is therefore considered appropriate that, in patients with XLH in transition from children to adults, burosumab be administered according to the dosage regimen for children until they reach the bone age of adults and, after that, the dosage regimen be switched to that of adults as appropriate, depending on the patient's conditions.

PMDA's view on the dosage regimen in adult and pediatric patients with XLH based on Sections 7.R.6.1.1 and 7.R.6.1.2:
Judging from the results of the clinical studies, the following dosage regimens are acceptable: (1) adult patients with XLH start treatment with burosumab 1 mg/kg Q4W (the dose for each patient is calculated from the baseline body weight and rounded to the nearest 10 mg, up to 90 mg), and the dose is decreased appropriately depending on the serum phosphorus concentration, symptoms, etc.; pediatric patients with XLH start treatment with burosumab 0.8 mg/kg Q2W, and the dose is adjusted appropriately depending

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[51] The population pharmacokinetics/pharmacodynamics model was constructed using Phoenix NLME v.7. The following sigmoid E_{max}, which included body weight as the fixed effect, was employed. $Phosp = E0 + (simC_{KRN23}^{\gamma} \cdot E_{max})/EC_{50}^{\gamma} + simC_{KRN23}^{\gamma})$, where Phosp is serum phosphate concentration, E0 is baseline serum phosphate concentration, EC_{50} is serum burosumab concentration at 50% effective concentration, E_{max} is concentration with the maximal effect, $simC_{KRN23}$ is estimated serum burosumab concentration, and γ is Hill coefficient.

[52] A body weight distribution model of adolescents aged 12 to 17 years was prepared based on the baseline body weight of pediatric aged 1 to 12 years and adult patients with XLH. Using this model, body weight of each patient in the hypothetical population of patients aged 12 to 17 years with XLH was generated in a randomized manner. Those patients with body weight within 90% CI were included in the hypothetical population of patients aged 12 to 17 years (n = [redacted]) with XLH, and results of burosumab administration using each dosage regimen to [redacted] patients were simulated.

on the serum phosphorus concentration, symptoms, etc., with the maximum dose being 2 mg/kg (up to 90 mg). For patients with XLH during the transition from childhood to adulthood, the patient population that remains uninvestigated in clinical studies, it is important to focus attention on the impact on the growth of pediatric patients with XLH during treatment. According to a population pharmacokinetic/pharmacodynamic simulation, serum phosphorus concentration is expected to increase within a certain range, both by the dosage regimen for children and by the one for adults. As proposed by the applicant, healthcare professionals should be advised to switch the pediatric dosage regimen to the adult regimen in consideration of the patient's bone maturation age.

As discussed in Section "7.R.5 Indication," burosumab may be indicated for FGF23-related hypophosphatemic rickets/osteomalacia, including not only XLH and TIO but also other diseases causing excess FGF23 production. While diseases other than XLH and TIO have not been investigated in the clinical studies, the applicant explained that the dosage regimen for diseases with gene mutation other than TIO should be the same as that for XLH, for the following reasons:

- XLH and other FGF23-related hypophosphatemic rickets/osteomalacia excluding TIO are classified as gene mutation-induced congenital diseases which develop in childhood. The diseases are treated with oral phosphate and active vitamin D_3 as with XLH.

- TIO is an acquired disease which develops mostly in adulthood, accompanying a higher FGF23 concentration than other diseases and often becomes severe. Thus, TIO has characteristics different from FGF23-related hypophosphatemic rickets/osteomalacia of congenital origin.

The applicant's explanation is generally acceptable, and the use of the XLH dosage regimen for gene mutation-induced diseases other than TIO is possible. In the post-marketing setting, data on burosumab should be collected from patients with these diseases to verify the safety and efficacy of burosumab in this patient population [see Section "7.R.8 Post-marketing investigations"].

7.R.6.2 Dosage and administration in patients with TIO

The applicant's explanation:

TIO is an acquired disease. FGF23 is produced heterotopically in localized tumor, and serum FGF23 concentration is particularly high as compared with congenital diseases such as XLH. Therefore, it is important that the dosage regimen for TIO be different from that for XLH, etc. In Study UX023T-CL201, the first study in patients with TIO, burosumab was administered once every 4 weeks as was the case with adult patients with XLH. However, the starting dose was 0.3 mg/kg, which was decreased or increased by 0.2 or 0.3 mg/kg depending on the serum phosphorus concentration up to 2 mg/kg. The dose adjustment was performed due to the possibility of the greater inter-individual variability in response to burosumab than that in XLH, and for the safety of patients. In the subsequent Study KRN23-002, which was the first clinical study in Japanese and Korean patients with TIO, the starting dose of 0.3 mg/kg was used for the safety of the patients, as was the case with the foreign study. In Study KRN23-002, serum phosphorus concentration at each evaluation time point, the primary endpoint, increased after burosumab administration, with the difference from the baseline level being almost constant from Week 24 (Figure 2). Similar results were obtained from Study UX023T-CL201 (Figure 3).

Serum phosphorus concentration exceeded the upper limit of normal (4.5 mg/dL) in 1 patient of Study KRN23-002. Serum phosphorus concentration was 4.6 mg/dL at Week 6. The next dosing (Week 8) was skipped, but the serum phosphorus concentration at Week 12 was within the normal range, and the treatment was resumed at the reduced dose of 0.1 mg/kg. Baseline serum phosphorus concentration was 2.7 mg/dL, which was above the lower limit of normal (2.5 mg/dL).

In Study KRN23-002, the doses almost reached a plateau around Week 36. As a result of further dose adjustment, the average dose at Week 64 onward was approximately 1 mg/kg, which was the same as the starting dose in adult patients with XLH. However, unlike in adult patients with XLH, the dose for individual patients varied widely in the range between 0.1 and 2.0 mg/kg, with the dose in more than half of patients being ≥1 mg/kg (Table 72).

Table 72. Changes in dose over time in Study KRN23-002[a)]

Evaluation time point	Dose (mg/kg)										
	0	0.1	0.3	0.6	0.8	1.0	1.2	1.4	1.6	1.8	2.0
Week 0	0 (0)	0 (0)	100 (13)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Week 4	0 (0)	0 (0)	46.2 (6)	53.8 (7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Week 12	0 (0)	7.7 (1)	15.4 (2)	30.8 (4)	15.4 (2)	30.8 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Week 24	0 (0)	15.4 (2)	7.7 (1)	23.1 (3)	7.7 (1)	23.1 (3)	7.7 (1)	0 (0)	7.7 (1)	0 (0)	0 (0)
Week 36	0 (0)	7.7 (1)	15.4 (2)	23.1 (3)	7.7 (1)	15.4 (2)	7.7 (1)	0 (0)	7.7 (1)	0 (0)	7.7 (1)
Week 48	0 (0)	7.7 (1)	15.4 (2)	15.4 (2)	15.4 (2)	7.7 (1)	0 (0)	15.4 (2)	7.7 (1)	0 (0)	7.7 (1)
Week 64	0 (0)	7.7 (1)	15.4 (2)	15.4 (2)	0 (0)	23.1 (3)	0 (0)	7.7 (1)	15.4 (2)	0 (0)	7.7 (1)
Week 88	7.7 (1)	7.7 (1)	15.4 (2)	7.7 (1)	0 (0)	15.4 (2)	7.7 (1)	7.7 (1)	0 (0)	15.4 (2)	7.7 (1)

Percentage of patients (number of patients)
a) n =13

Because TIO is an acquired disease accompanied by other pathological conditions (e.g., cancer). There are many diseases to be excluded before TIO is confirmed, which often increase its severity with diverse clinical manifestations. Therefore, patients should be treated at the maximal possible starting dose and subsequent doses promptly and appropriately adjusted. In Study KRN23-002, 10 of 13 patients underwent dose increase, but the increment in serum phosphorus concentration was very small when the dose was increased in a stepwise manner. In 1 patient, the primary disease became aggravated without any increase in serum phosphorus concentration, and the treatment was discontinued before the dose was increased to a sufficient level. There were 2 patients who underwent dose increase, for which one patient spent 30 weeks and the other 34 weeks until serum phosphorus concentration reached 2.0 mg/dL. Thus, the starting dose of 0.3 mg/kg with subsequent dose increase by 0.2 or 0.3 mg/kg will consume too much time for patients requiring a high dose to reach the optimal dose, resulting in delayed improvement in serum phosphorus concentration and bone metabolism, possibly aggravating symptoms.

Because of such possible scenario, burosumab therapy should preferably be started at the highest possible dose that is higher than the starting dose in Study KRN23-002 but is free from safety concerns,

and followed by rapid dose escalation. On the other hand, Study KRN23-002 showed that there were quite a few patients for whom the optimal dose found to be <1 mg/kg. The starting dose should preferably be lower to some extent, instead of following the starting dose for adult patients with XLH.

The starting dose of 0.3 mg/kg is considered well tolerated in patients with TIO, based on the results of Study KRN23-002. In Study KRN23-001 in adult patients with XLH, the maximum increase in serum phosphorus concentration from baseline was 0.77 mg/dL, 0.94 mg/dL, and 1.03 mg/dL, respectively, after the administration of 0.3 mg/kg, 0.6 mg/kg, and 1 mg/kg of burosumab. The results indicate that the difference among these doses is unlikely to cause an excessive increase in serum phosphorus concentration. Thus, the starting dose of ≥0.3 mg/kg is unlikely to cause a frequent increase in serum phosphorus concentration above the upper limit of normal in patients with hypophosphatemia. In Study KRN23-INT-002 in adult patients with XLH, treatment was started from a low dose of ≤0.6 mg/kg, followed by adjustment as necessary. As a result, the dose of burosumab at Week 48 was <1 mg/kg in 6 of 19 patients. In contrast, in Studies UX023-CL303 and UX023-CL304 in which 1 mg/kg was administered to all adult patients with XLH, dose reduction before Week 48 was necessitated in only 11 patients (9 patients due to an increase in serum phosphorus concentration) of 134 receiving burosumab in Study UX023-CL303 and in none of the patients in Study UX023-CL304. These results suggest that, even if the starting dose is above the optimal dose for some patients, it is unlikely to frequently increase serum phosphorus concentration to above the upper limit of normal. In 10 patients who underwent a dose increase in Study KRN23-002, no significant difference was observed in the degree of the increase in serum phosphorus concentration after the administration of 0.6 mg/kg, 1 mg/kg, 1.6 mg/kg, and 2 mg/kg. In Study UX023T-CL201, 1 patient received 1 mg/kg after 0.6 mg/kg, but no excessive increase in serum phosphorus concentration was observed. These results suggest that a dose increase by ≥0.2 mg/kg in patients with serum phosphorus concentration below the normal levels is unlikely to increase serum phosphorus concentration above the upper limit of normal. Thus, there are no safety problems in increasing burosumab by 0.5 mg/kg for patients with TIO. The possibility cannot be excluded that an unexperienced starting dose increases serum phosphorus concentration excessively. However, in Study UX023-CL303, even in 9 patients in whom serum phosphorus concentration exceeded the normal levels, necessitating treatment interruption or dose reduction, subsequent serum phosphorus concentration was maintained within the normal range without any other adverse events associated with the temporary hyperphosphatemia, ensuring safety. Thus, such risk is controllable by monitoring serum phosphorus concentration during the early stage of treatment.

Based on the above, the appropriate dosage regimen of burosumab for patients with TIO starts with 0.5 mg/kg Q4W, which is adjusted as necessary depending on serum phosphorus concentration and patient condition, up to 2 mg/kg. The increment of 0.5 mg/kg will allow prompt adjustment to an appropriate dose in patients with severe TIO.

PMDA's view:
In the clinical studies in patients with TIO, there were a certain number of patients who required a higher dose of burosumab than the starting dose stipulated in the study, and some of them discontinued the study due to inadequate improvement in symptoms by the stipulated dosage regimen. Thus, some patients with TIO may need to be treated with a high dose of burosumab from the early stage of the

treatment. On the other hand, there are a certain number of patients whose serum phosphorus concentration can be controlled at a low dose of burosumab. Also, according to the applicant, based on the results of clinical studies in patients with XLH, increased serum phosphorus concentration caused by excess dose of burosumab is controllable. However, patients with TIO have greater interindividual differences in severity than those with XLH, and it is inappropriate to determine the starting dose in patients with TIO based on the results of clinical studies in patients with XLH. Thus, there is no adequate rationale for the starting dose of 0.5 mg/kg for burosumab therapy in patients with TIO as proposed by the applicant. The dose of 0.3 mg/kg was used in the clinical studies in patients with TIO, and the efficacy and safety of burosumab in patients with TIO were confirmed in these studies. Thus, the starting dose of burosumab in patients with TIO should be 0.3 mg/kg. Similarly, the increment by 0.5 mg/kg, which is not stipulated in the clinical studies in patients with TIO, also lacks rationale. At the same time, the protocol-specified 0.2-mg/kg increment required much time to improve symptoms in a certain number of patients with TIO, and requiring all patients to undergo the 0.2-mg/kg increment will also pose an issue. Given this situation, the dose adjustment method specified in the clinical studies should be communicated, and the package insert should advise that the dose be carefully increased according to serum phosphorus concentration and clinical condition monitored. Because of the limited experience in use of burosumab in patients with TIO, post-marketing data should be collected on the safety and efficacy of burosumab in the patient population treated with the above dosage regimens. The conclusion by PMDA will be finalized, taking the comments from the Expert Discussion into account.

7.R.6.3 Concomitant use with oral phosphate and active vitamin D_3

The applicant's explanation about the concomitant use of burosumab with oral phosphate and active vitamin D_3:

The conventional treatment with oral phosphate or active vitamin D_3 works only to supplement phosphate excreted by FGF23. Burosumab improves hypophosphatemia by neutralizing excess FGF23, and burosumab monotherapy has been shown to be actually effective and safe in the clinical studies. If burosumab is administered in combination with oral phosphate or active vitamin D_3 to patients with FGF23-related hypophosphatemic rickets/osteomalacia, phosphate will be supplemented under the condition where burosumab neutralizes the action of FGF23 so that phosphate-excreting function is improving, raising a potential risk of hyperphosphatemia. Also, in case of persistent hyperphosphatemia, heterotopic calcification and other complications may occur. The degree of increase in serum phosphorus concentration is hardly estimated when burosumab is concomitantly used with oral phosphate or active vitamin D_3. No clinical study was conducted on the combination of burosumab with oral phosphate or active vitamin D_3, of which efficacy or safety has not been established. A majority of patients enrolled in the clinical studies of burosumab did not adequately responded to oral phosphate or active vitamin D_3, but switching to burosumab was shown to be effective and safe. Accordingly, the concomitant use of burosumab with oral phosphate or active vitamin D_3 is not recommended.

PMDA's view:

In the clinical studies of burosumab, the efficacy and safety of burosumab monotherapy were confirmed, while the efficacy and safety of the combination of burosumab with oral phosphate or active vitamin D_3 were not investigated. As explained by the applicant, burosumab should basically be administered alone because of (1) the difficulty in estimating the degree of increase in serum phosphorus concentration in

the combination use of burosumab with oral phosphate or active vitamin D_3 and (2) a risk of heterotopic calcification posed by persistent hyperphosphatemia. On the other hand, the risk of heterotopic calcification caused by persistent hyperphosphatemia can be controlled by the measurement of serum phosphorus concentration and intact PTH concentration, etc. and by image monitoring. Given these, how cautionary advice should be given appropriately on the concomitant use of burosumab with oral phosphate or active vitamin D_3 should be discussed. This conclusion by PMDA on cautionary advice will be finalized, taking the comments from the Expert Discussion into account.

7.R.7 Patient population with special characteristics

7.R.7.1 Patients with renal impairment

PMDA asked the applicant to explain the efficacy and safety of burosumab in patients with renal impairment.

The applicant's explanation:

Patients with mild to moderate renal impairment were enrolled in Study UX023-CL303 in adult patients with XLH and in Study KRN23-002 in patients with TIO. The efficacy and safety of burosumab were investigated by severity of renal impairment (normal, baseline eGFR [mL/min/1.73 m^2] ≥90; mild, ≥60 and <90; moderate, ≥30 and <60), as described below. In Study UX023-CL304 in adult patients with XLH and Study UX023-CL301 in pediatric patients with XLH, baseline eGFR was normal in all patients who were tested, precluding the investigation by severity of renal impairment.

In the burosumab group of Study UX023-CL303, 62 patients had normal renal function and 6 patients had mild renal impairment. There were no patients with moderate renal impairment. Time-course changes in serum phosphorus concentration and change from baseline did not significantly differ between groups by severity of renal impairment. A total of 121 patients with normal renal function and 13 patients with mild renal impairment received burosumab throughout the entire treatment period. According to the safety analysis, the incidences of adverse events and adverse drug reactions were 97.5% (118 of 121) and 53.7% (65 of 121), respectively, in patients with normal renal function, and 100% (13 of 13) and 69.2% (9 of 13), respectively, in patients with mild renal impairment, showing no significant difference between the two groups. In contrast, serious adverse events occurred in 9.9% (12 of 121) of patients with normal renal function and 23.1% (3 of 13) of patients with mild renal impairment, showing a higher frequency in patients with mild renal impairment. Similarly, the incidences of hyperphosphatemia-related events and heterotopic calcification were higher in patients with mild renal impairment than in patients with normal renal function, i.e., 5.0% (6 of 121) for both types of adverse events in patients with normal renal function, and 15.4% (2 of 13) and 23.1% (3 of 13), respectively, in patients with mild renal impairment.

In Study KRN23-002, 5 patients had normal renal function, 4 patients had mild renal impairment, and 3 patients had moderate renal impairment. Patients with moderate renal impairment, serum phosphorus concentration was lower than in other subgroups, but time-course changes were similar. The incidences of adverse events and adverse drug reactions were 80.0% (4 of 5) and 40.0% (2 of 5), respectively, in patients with normal renal function, 100% (4 of 4) and 40.0% (2 of 5), respectively, in patients with mild renal impairment, and 100% (3 of 3) and 33.3% (1 of 3), respectively, in patients with moderate renal

impairment, showing no significant difference among the subgroups. The incidence of serious adverse events was 0% (0 of 5) in patients with normal renal function, 50.0% (2 of 4) in patients with mild renal impairment, and 33.3% (1 of 3) of patients with moderate renal impairment, being higher in patients with mild or moderate renal impairment than in patients with normal renal function. Neither hyperphosphatemia-related events nor heterotopic calcification-related events occurred in any subgroup.

The above results showed a slight difference in time-course changes in serum phosphorus concentration but not in the change from baseline, which suggests no difference in the efficacy of burosumab among patients with different degree of renal impairment. Among these patients, the incidence of serious adverse events was higher in patients with mild or moderate renal impairment both in Studies UX023-CL303 and KRN23-002, but the difference was minor and does not require extra attention during burosumab therapy. In Study UX023-CL303, the incidences of hyperphosphatemia-related events and heterotopic calcification-related events were higher among patients with mild impairment. The relationship between Hyperphosphatemia-related events were investigated based on serum phosphorus concentration, an efficacy parameter of burosumab. There was no tendency toward increased serum phosphorus concentration with a mild decrease in eGFR, requiring no immediate attention during therapy. In contrast, the incidence of heterotopic calcification-related events increased, suggesting the need for attention during burosumab therapy. However, there were no serious adverse events or adverse events leading to treatment discontinuation, thus burosumab should be used with appropriate cautionary advice given on heterotopic calcification.

Most patients with severe renal impairment or end stage renal failure have hyperphosphatemia caused by the decreased phosphate excretion due to decreased urine volume. It is assumed that there are not many patients with FGF23-related hypophosphatemic rickets/osteomalacia who have severe renal impairment or end stage renal failure. Even so, these patients have a potential risk of hyperphosphatemia in the event of the use of burosumab because of impaired renal function. Persistent hyperphosphatemia causes heterotopic calcification of the kidney, etc., which may further aggravate renal impairment. There is no use experience of burosumab in patients with severe renal impairment or end stage renal failure. In light of the increased incidence of heterotopic calcification-related events even in patients with mild impairment, the use of burosumab in patients with severe renal impairment or end stage renal failure should be avoided.

PMDA's view:
The safety data from patients with renal impairment suggest no significant safety problem, although there were only a limited number of patients with mild or moderate renal impairment who were enrolled in clinical studies. However, based on a slight increase in the incidence of heterotopic calcification-related events in patients with renal impairment in Study UX023-CL303, cautionary advice should be given on heterotopic calcification. The safety or efficacy of burosumab in patients with severe renal impairment or end stage renal failure were not investigated because they were not enrolled in clinical studies. Also, these patients are prone to increased serum phosphorus concentration, and persisting hyperphosphatemia raises a risk of heterotopic calcification. On the other hand, the risk of heterotopic calcification induced by persistent hyperphosphatemia is considered controllable by the monitoring of serum phosphorus concentration, intact PTH concentration, and images. In addition, in actual clinical

practice, patients who have experienced FGF23-related hypophosphatemia are treated with oral phosphate or active vitamin D_3, which may cause kidney calcification that poses a risk of the aggravation of renal impairment. These facts should also be taken into consideration. How advice on patients with renal impairment should be given will be finalized taking the comments from the Expert Discussion into account.

7.R.8 Post-marketing investigations

The applicant's explanation:

Because of the limited number of Japanese patients who received burosumab, a specified use-results survey will be conducted covering all patients receiving burosumab (all-case surveillance) to investigate the safety and efficacy. The survey period will be 8 years after the market launch, with a 1 year follow-up period for each patient. Most adverse events occurred for the first time within 11 weeks after the start of burosumab administration in the clinical studies in patients with XLH. Serum phosphorus concentration that indicates efficacy exceeded the lower limit of normal and remained stable before Week 24. Accordingly, the follow-up period has been planned to be 1 year. Results of the long-term treatment up to 208 weeks in adults with XLH, up to160 weeks in pediatric patients with XLH, and up to 216 weeks in patients with TIO will be obtained from the ongoing studies.

PMDA's view:

There are only a limited number of patients with FGF23-related hypophosphatemic rickets/osteomalacia. As proposed by the applicant, post-marketing surveillance should cover all patients receiving burosumab to obtain information as promptly as possible on the safety and efficacy in patients with FGF23-related hypophosphatemic rickets/osteomalacia. Clinical studies can provide only limited safety and efficacy data, particularly from patients with TIO, and no information is available on the safety and efficacy of burosumab in patients with diseases other than XLH and TIO. Therefore, the post-marketing surveillance should be designed in a way that allows access to data on these patient populations appropriately.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The inspection is currently ongoing. Results and the conclusion of PMDA will be reported in the Review Report (2).

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The inspection is currently ongoing. Results and the conclusion of PMDA will be reported in the Review Report (2).

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that burosumab has efficacy in the treatment of FGF23-related hypophosphatemic rickets/osteomalacia, and that burosumab has acceptable safety in view of its benefits. Burosumab is a human IgG1 monoclonal antibody targeted at FGF23, which offers

a new treatment option for patients with FGF23-related hypophosphatemic rickets/osteomalacia. Thus the product is of clinical significance.

PMDA has concluded that burosumab may be approved if burosumab is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

August 7, 2019

Product Submitted for Approval

Brand Name	Crysvita Subcutaneous Injection 10 mg Crysvita Subcutaneous Injection 20 mg Crysvita Subcutaneous Injection 30 mg
Non-proprietary Name	Burosumab (Genetical Recombination)
Applicant	Kyowa Kirin Co., Ltd. (formerly Kyowa Hakko Kirin Co., Ltd.)
Date of Application	January 7, 2019

List of Abbreviation

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized in the following. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Clinical positioning of burosumab

PMDA's view:

Frequent administration of oral phosphate and active vitamin D_3 is the only accessible symptomatic drug therapy for FGF23-related hypophosphatemic rickets/osteomalacia. This conventional therapy has safety issues such as secondary or tertiary hyperparathyroidism and kidney calcification as well as a compliance issue. Burosumab has a novel mechanism of action that neutralizes the effect of excess FGF23 causing FGF23-related hypophosphatemic rickets/osteomalacia. Burosumab thus has a clinical significance as a therapeutic option in its clinical use to improve the symptoms of FGF23-related hypophosphatemic rickets/osteomalacia.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.2 Efficacy

1.2.1 Efficacy in adult patients with XLH

PMDA's view:

In the global Study UX023-CL303 in adult patients with XLH, the percentage of patients achieving mean serum phosphorus above the lower limit of normal (2.5 mg/dL) at the midpoint of each treatment cycle between baseline and Week 24, the primary efficacy endpoint, was significantly higher in the

burosumab group than in the placebo group, and the elevated serum phosphorus concentration tended to be maintained during the long-term treatment. In addition, clinical symptoms (pain, motor function, and physical function) and fracture/pseudofracture tended to improve. On the basis of these observations, burosumab is effective in adult patients with XLH.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.2.2 Efficacy in pediatric patients with XLH

PMDA's view:

In the global Study UX023-CL301 in pediatric patients aged 1 to 12 years with XLH, RGI-C global score at Week 40, which is the primary endpoint and an indicator of rachitic symptoms, improved significantly in the burosumab group than in the control group (treated with oral phosphate and active vitamin D_3). Also, the mean serum phosphorus concentration did not exceed the lower limit of normal at any measuring time point in the control group but exceeded the lower limit of normal at almost all measuring time points in the burosumab group. These outcomes were maintained up to Week 64. Similarly, in the Japanese Study KRN23-003 in Japanese pediatric patients with XLH, which was an open-label uncontrolled study, RGI-C global score and serum phosphorus concentration at Week 40 showed a tendency toward improvement after burosumab administration. There results demonstrate the efficacy of burosumab in pediatric patients with XLH.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.2.3 Efficacy in patients with TIO

PMDA's view:

Because of the limited number of patients with TIO even as compared with those with XLH, and that precluded a comparative study. TIO is primarily characterized by hypophosphatemia due to impaired bone mineralization caused by excess FGF23, which is the same as XLH. Therefore, it was unavoidable to evaluate the efficacy of burosumab in TIO based on the results of uncontrolled global Study KRN23-002 and the foreign Study UX023T-CL201. In these studies, mean serum phosphorus concentration increased after the start of burosumab administration and remained above the lower limit of normal by appropriate dose adjustment. In addition, improved osteomalacia-associated histomorphological findings and a trend toward improving motor function-related clinical symptoms of osteomalacia. On the basis of these observations, burosumab is effective in patients with TIO.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.3 Safety

PMDA's view:

In Study UX023-CL303 in adult patients with XLH, the incidence of adverse events did not differ significantly between the placebo group and the burosumab group. In Studies UX023-CL303 and UX023-CL304, no particular safety problems were observed in long-term treatment with burosumab. In Study UX023-CL301 in pediatric patients aged 1 to 12 years with XLH, the incidence of adverse events tended to be higher in the burosumab group than in the control group receiving oral phosphate and active

vitamin D_3, but the observed difference was most likely due to the route of administration (subcutaneous vs. oral), and the events identified or their severity in the burosumab group were not particularly problematic. Also, the safety profile in patients with TIO in each clinical study did not have any particular problem. The action mechanism of burosumab and the results of the Japanese and foreign clinical studies revealed adverse events requiring attention during burosumab therapy, namely, hypersensitivity, hyperphosphatemia-related events, heterotopic calcification-related events, and restless legs syndrome. However, burosumab has acceptable safety where appropriate safety measures, such as the provision of cautionary advice, are taken.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.4 Indication

PMDA's view:

The proposed indication of burosumab is "FGF23-related hypophosphatemic rickets/osteomalacia." Burosumab is shown to have efficacy and acceptable safety in the treatment of XLH and TIO in the clinical studies, and thus the proposed indication of burosumab with clearly specified XLH and TIO is appropriate. Among the diseases included in FGF23-related hypophosphatemic rickets/osteomalacia, diseases other than XLH and TIO were not investigated in clinical studies. However, burosumab is expected to be effective to a certain extent in these diseases as well because they also are characterized by impaired bone mineralization due to excess FGF23 production-associated hypophosphatemia, and burosumab has the pharmacological effect of neutralizing excess FGF23. Moreover, because of the extremely limited number of patients with diseases other than XLH and TIO even as compared with XLH and TIO, a clinical study involving this patient population is infeasible. Given these, "FGF23-related hypophosphatemic rickets/osteomalacia" is the appropriate indication of burosumab. Because of the lack of safety and efficacy data of patients with non-XLH or -TIO, safety and efficacy in these patients receiving burosumab should be confirmed after the market launch.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.5 Dosage and administration

1.5.1 Dosage and administration in patients with XLH, etc.

PMDA's view:

Based on the dosage regimens determined in the clinical studies in adult and pediatric patients with XLH and the results obtained from these studies, the following are the appropriate dosage regimens of burosumab: (1) for adult patients with XLH, the starting dose of 1 mg/kg (90 mg at the maximum) administered once every 4 weeks. The dose should be decreased as necessary according to serum phosphorus concentration, clinical symptoms, etc.; (2) for pediatric patients with XLH, the starting dose of 0.8 mg/kg of burosumab administered once every 2 weeks. The dose should be adjusted as necessary according to serum phosphorus concentration, clinical symptoms, etc., with the maximum dose being 2 mg/kg (90 mg/dose at the maximum). In terms of patients with XLH who are in transition from childhood to adulthood (13-17 years of age), the age group not investigated in the clinical studies, the applicant explained that it is important to pay attention to the effect of treatment on growth during the pediatric period, and that serum phosphorus concentration is expected to increase within a certain range

regardless of whether by the dosage regimen for children or adults. Given these observations, the dosage regimen for children should be switched to that for adults when they reach adult bone age, and this should be mentioned in the “Precautions for Dosage and Administration” section.

Based on the explanation by the applicant on non-XLH or -TIO diseases uninvestigated, the diseases with gene mutations other than TIO may be treated according to the same dosage regimen as used for XLH for the following reasons: FGF23-related hypophosphatemic rickets/osteomalacia including XLH but not TIO are classified as gene mutation-induced, childhood-onset congenital disease, and the disease is treated with oral phosphate and active vitamin D_3, as is the case with XLH. In contrast, TIO is an acquired disease, which develops mostly during adulthood, shows a higher FGF23 concentration than other diseases, and is often severe, thus showing characteristic features different from those of FGF23-related hypophosphatemic rickets/osteomalacia of congenital origin.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.5.2 Dosage and administration in patients with TIO

PMDA’s view:

In the clinical studies in patients with TIO, the starting dose was 0.3 mg/kg, and the dose was adjusted by 0.2 or 0.3 mg/kg depending on the serum phosphorus concentration up to 2 mg/kg. However, the applicant proposed to start therapy at 0.5 mg/kg with dose increase by 0.5 mg/kg for the reasons including the following: TIO often turns severe with a variety of clinical symptoms, and it is essential to start the treatment at the highest dose possible and to adjust to the appropriate dose promptly. There were patients who required a higher dose of burosumab than protocol-specified and, some of these patients did not response to the study dosage regimen, resulting in study discontinuation. These results suggest the presence of patients who need to be treated at a high dose from the early stage of the treatment. At the same time, the clinical studies in patients with TIO with the starting dose of 0.3 mg/kg demonstrated the efficacy and safety of burosumab in patients with TIO, and the disease could be controlled by a low dose of burosumab in a certain number of patients. Thus, there is no sufficient reason for the starting dose of burosumab at 0.5 mg/kg for patients with TIO, and these patients should start treatment at 0.3 mg/kg as specified in the clinical studies.

There is also no sufficient reason for the increment of 0.5 mg/kg, because it was not specified in the clinical studies in patients with TIO. However, the adjustment by 0.2-mg/kg as per the study protocol required longer time to improve the symptoms, etc. in a certain number of patients with TIO. Thus specifying the increment/decrement uniformly at 0.2 mg/kg will also raise problems. Therefore, the package insert should provide the information on how dose adjustment was implemented in the clinical studies along with cautionary advice so that the dose be carefully increased according to serum phosphorus concentration and general condition monitored. Because of the limited use experience of burosumab in patients with TIO, safety and efficacy information on burosumab should be collected in the post-marketing setting from patients with TIO treated with the above dosage regimens.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

On the basis of the discussions in Sections 1.5.1 and 1.5.2, PMDA asked the applicant to modify the dosage and administration as shown below, and to add the following note in the "Precaution for Dosage and Administration" section, and confirmed that the applicant responded appropriately.

Dosage and administration
FGF23-related hypophosphatemic rickets/ osteomalacia (except for tumor-induced osteomalacia)
The usual adult dosage is 1 mg/kg of burosumab (genetical recombination) injected subcutaneously once every 4 weeks. Each dose should not exceed 90 mg. The dose may be adjusted according to serum phosphorus concentration, clinical symptoms, etc.

The usual pediatric dosage is 0.8 mg/kg of burosumab (genetical recombination) injected subcutaneously once every 2 weeks. The dose may be adjusted according to serum phosphorus concentration, clinical symptoms, etc., up to the maximum of 2 mg/kg. However, the dose should not exceed 90 mg.

Tumor-induced osteomalacia
The usual adult dosage is 0.3 mg/kg of burosumab (genetical recombination) injected subcutaneously once every 4 weeks. The dose may be adjusted according to serum phosphorus concentration, clinical symptoms, etc., up to the maximum of 2 mg/kg.

Precautions for Dosage and Administration (excerpt)
For patients with FGF23-related hypophosphatemic rickets who have reached the bone age of ≥17 years (boys) or ≥15 years (girls), the adult regimen should be used depending on their condition.

1.5.3 Concomitant use with oral phosphate or active vitamin D_3

PMDA's view:
In the clinical studies on burosumab, the efficacy and safety of burosumab monotherapy were confirmed, whereas which is not investigated in combination with oral phosphate or active vitamin D_3. It is difficult to estimate to what extent serum phosphorus concentration increases when burosumab is administered in combination with oral phosphate or active vitamin D_3. In addition, persisting hyperphosphatemia raises a risk of heterotopic calcification. Therefore, burosumab should basically be administered alone. At the same time, the risk of heterotopic calcification caused by persisting hyperphosphatemia can be controlled by measuring of serum phosphorus concentration and intact PTH concentration and image monitoring. Given these observations, while keeping the option open of not contraindicating the combination use of burosumab with oral phosphate or active vitamin D_3, an appropriate way to give cautions against such use should be discussed.

The following comments, etc., were raised about the way to give cautions against the matter from the expert advisors at the Expert Discussion:

- The combination of burosumab with oral phosphate and active vitamin D_3 may cause hyperphosphatemia. The efficacy and safety of the combination therapy were not investigated in the clinical studies, and the use of burosumab with these concomitant drugs is thus not recommended. However, when the therapy with oral phosphate and active vitamin D_3 is discontinued to be switched

to burosumab, which is started at a low dose and followed by gradual dose increase, burosumab may not increase serum phosphorus concentration sufficiently and worsen the symptoms. Therefore, temporary use of burosumab with the concomitant drugs may be necessary during the switching period.

- Burosumab is basically intended to be used alone. However, the clinical setting may have patients who need the combination therapy of burosumab with oral phosphate and active vitamin D_3.

- Although the combination use has possible risks of hyperphosphatemia and heterotopic calcification, disease control may be difficult solely by burosumab in some patients, particularly in those with TIO, due to individual variability in the pathology. Therefore, the combination therapy should not be contraindicated in the package insert, unlike the applicant's proposal. Instead, the risk of heterotopic calcification due to persistent hyperphosphatemia in patients treated with the combination therapy should be communicated, along with the advice on appropriate monitoring of serum phosphorus concentration, intact PTH, and images.

Taking account of the comments of the expert advisors, PMDA instructed the applicant to give the following cautionary advice in the package insert: (1) the use of burosumab with concomitant oral phosphate and active vitamin D_3 should be avoided whenever possible; (2) the combination therapy was not investigated in any clinical study; and (3) the combination therapy may cause hyperphosphatemia. PMDA confirmed that the applicant took appropriate measures.

1.6 Patients with special characteristics (patients with renal impairment)

PMDA's view:

Although an extremely limited number of patients with mild or moderate renal impairment were enrolled in the clinical studies, the obtained data did not suggest any significant safety problem. However, in Study UX023-CL303 in adult patients with XLH, the incidence of heterotopic calcification-related events was slightly higher in patients with renal impairment than in patients without renal impairment. Therefore, caution should be paid to heterotopic calcification in patients with renal impairment. Patients with severe renal impairment or end stage renal failure were not enrolled in the clinical studies, precluding the assessment of safety and efficacy in this patient group. These patients are prone to an increase in serum phosphorus concentration and have a risk of heterotopic calcification due to persistent hyperphosphatemia. On the other hand, the risk of heterotopic calcification caused by persisting hyperphosphatemia can be controlled by monitoring of serum phosphorus concentration, intact PTH concentration, and images. Furthermore, in actual clinical practice patients who have FGF23-related hypophosphatemia are treated with oral phosphate or active vitamin D_3, although which may aggravate renal impairment due to kidney calcification. These facts should be taken into account when determining how cautionary advice on patients with renal impairment be expressed.

At the Expert Discussion, the following comment was raised from expert advisors on how cautionary advice should be given: Because of the possibility that burosumab is indicated even for patients with renal impairment, burosumab should not be contraindicated for patients with severe renal impairment with no exception. The use of burosumab should preferably be allowed for these patients based on the

risk-benefit balance weighted the in the clinical setting, with requirements for close monitoring of serum phosphorus concentration, intact PTH, and images. At the same time, the following opposing comment was raised as well: As supported by the data of Study UX023-CL303, patients with renal impairment have a high risk of hyperphosphatemia, possibly resulting in heterotopic calcification caused by burosumab. In addition, unexpected physiological responses might occur in patients with severe renal impairment or end stage renal failure. Therefore, burosumab should be contraindicated for this patient group as proposed by the applicant.

Accordingly, PMDA asked the applicant to explain the approximate percentage of patients with severe renal impairment or end stage renal failure among patients with FGF23-related hypophosphatemic rickets/osteomalacia, and to explain the appropriateness of contraindicating burosumab for these patients from the viewpoint of risk-benefit balance in the burosumab therapy.

The applicant's explanation:
Most patients with severe renal impairment or end stage renal failure present with decreased phosphate excretion due to decreased urine volume associated with compromised renal function, causing hyperphosphatemia. It is therefore very unlikely that patients with severe renal impairment or end stage renal failure experience FGF23-related hypophosphatemic rickets/osteomalacia. Even if there are patients with FGF23-related hypophosphatemic rickets/osteomalacia who have severe renal impairment or end stage renal failure, these patients are expected to have serum phosphorus concentration that is high enough to develop hyperphosphatemia. There will be little benefit of these patients from burosumab therapy. In addition, the possibility cannot be excluded that, in these patients, burosumab therapy may cause a more rapid and extensive increase in serum phosphorus concentration than that observed in the patient populations investigated in the clinical studies. Since these patients are devoid of normal renal function, they may have an increased risk of hyperphosphatemia and heterotopic calcification to kidneys and other organs if burosumab is administered, given the mechanism of the increase in serum phosphorus concentration induced by burosumab. Treatment with oral phosphate and active vitamin D_3, the conventional treatment, is feasible in this patient group, and burosumab should be contraindicated for patients with severe renal impairment or end stage renal failure.

PMDA accepted the applicant's explanation.

1.7 Risk management plan (draft)

Based on its review presented in Section "7.R.8 Post-marketing investigations" of the Review Report (1) and the comments raised from the expert advisors at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for burosumab should include the safety and efficacy specifications presented in Table 73, and that the applicant should implement additional pharmacovigilance activities and risk minimization activities presented in Tables 74 and 75.

Table 73. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
None	• Heterotopic calcification • Serious hypersensitivity reactions • Reproductive and developmental toxicity	• Safety in long-term treatment
Efficacy specification		
Efficacy in long-term treatment		

Table 74. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-results survey • Post-marketing clinical study[a)]	• Disseminate data gathered during early post-marketing phase vigilance.

a) The ongoing Studies KRN23-002, KRN23-003, and KRN23-004 (ongoing on Japanese and Korean subjects among subjects who have completed the global Study UX023-CL301, UX023-CL303, or UX023-CL304) will be reclassified as a post-marketing clinical study after approval.

Table 75. Outline of the specified use-results survey (draft)

Objective	To investigate the safety and efficacy of burosumab in clinical use
Survey method	Central registry system
Population	Patients with FGF23-related hypophosphatemic rickets/osteomalacia
Observation period	1 year
Planned sample size	All patients receiving burosumab (planned sample size, 250 subjects [including ≥30 patients with TIO])
Main survey items	Patient characteristics, use status of burosumab, adverse events, serum phosphorus concentration

Based on the above, PMDA instructed the applicant to investigate the safety and efficacy of burosumab after the market launch in an appropriate manner, to which the applicant agreed.

1.8 Data on quality

The document-based GLP/GCP inspection revealed that some of the records on the quality were not retained appropriately [see Section "2.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment"]. However, PMDA confirmed that the missing data does not affect the conclusion of the Review Report (1).

2. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

2.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The results showed that some parts of CTD 3.2.P.5.4 and 3.2.P.8.3 were not stored appropriately. PMDA concluded that the relevant data should be removed from the application documents submitted or any other countermeasure should be taken before PMDA reviews the documents.

2.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1-2, CTD 5.3.5.1-3, CTD 5.3.5.2-7, and CTD 5.3.5.2-8) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted. The following error was noted at the sponsor (in-country clinical care taker). Although it did not significantly affect the overall evaluation of the study, the error was notified to the sponsor (in-country clinical care taker) to request a corrective action.

Finding requiring corrective action

Sponsor (in-country clinical care taker)

- An error in the supply of the control drug to medical institutions and control

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration modified below, with the following conditions. The product is designated as an orphan drug with the re-examination period of 10 years. It is a biological product, and the drug product and its drug substance are both classified as powerful drugs.

Indication

FGF23-related hypophosphatemic rickets/osteomalacia

Dosage and administration

FGF23-related hypophosphatemic rickets/osteomalacia (except for tumor-induced osteomalacia)

The usual adult dosage is 1 mg/kg of burosumab (genetical recombination) injected subcutaneously once every 4 weeks. Each dose should not exceed 90 mg. The dose may be adjusted according to serum phosphorus concentration, clinical symptoms, etc. ~~The maximum dose is 1 mg/kg or 90 mg, whichever is lower.~~

The usual pediatric dosage is 0.8 mg/kg of burosumab (genetical recombination) injected subcutaneously once every 2 weeks. The dose may be adjusted according to serum phosphorus concentration, clinical symptoms, etc., up to the maximum of 2 mg/kg ~~or 90 mg, whichever is lower~~. However, the dose should not exceed 90 mg. ~~In pediatric patients with bone age of ≥17 years (boys) or ≥15 years (girls), the same dosage regimen as that for adults is used according to the patient's conditions.~~

Tumor-induced osteomalacia

The usual adult dosage is ~~0.5~~0.3 mg/kg of burosumab (genetical recombination) injected subcutaneously once every 4 weeks. The dose may be adjusted according to serum phosphorus concentration, clinical symptoms, etc., up to the maximum of 2 mg/kg.

(Crossed-out words are deleted from the applicant's proposal. Underline denotes additions to the applicant's proposal.)

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.

2. Since only a limited number of Japanese patients participated in the clinical studies of the product, the applicant is required to conduct a drug use-results survey involving all Japanese patients treated with the product after the market launch until data from a certain number of patients are gathered, to understand the characteristics of patients using the product and to promptly collect safety and efficacy data so that necessary measures are taken to ensure the proper use of the product.

Appendix

List of Abbreviations

$1,25(OH)_2D$	1,25-dihydroxy vitamin D
25(OH)D	25-hydroxyvitamin D
6MWT	Six-minute walk test
ADCC	Antibody dependent cellular cytotoxicity
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the drug serum concentration-time curve
BA	Bioavailability
BMI	Body mass index
Burosumab	Burosumab (Genetical Recombination)
CAL	Cells at the limit of *in vitro* cell age used for production
CDC	Complement dependent cytotoxicity
CE-SDS	Capillary electrophoresis-sodium dodecyl sulfate
CEX-HPLC	Cation exchange-high pressure liquid chromatography
C_{max}	Maximum serum concentration
CQA	Critical quality attribute
[redacted]	[redacted]
Crysvita	Crysvita Subcutaneous Injection 10 mg, Crysvita Subcutaneous Injection 20 mg, Crysvita Subcutaneous Injection 30 mg
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
ENS	Epidermal nevus syndrome
FAS	Full analysis set
FcRn	Neonatal Fc receptor
FcγR	Fc gamma receptor
FGF23	Fibroblast growth factor 23
FGFR	Fibroblast growth factor receptor
HCP	Host cell protein
HEK	Human embryonic kidney
HPLC	High performance liquid chromatography
[redacted]	[redacted]
Hyp mouse	Hypophosphatemic mouse
ICH	International council for harmonization of technical requirements for pharmaceuticals for human use
ICH Q5A (R1) Guideline	"Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin" (PMSB/ELD Notification No. 329, dated February 22, 2000)
ICH Q5B Guideline	"Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of R-DNA Derived Protein Products" (PMSB/ELD Notification No. 3, dated January 6, 1998)
ICH Q5D Guideline	"Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products" (PMSB/ELD Notification No. 873, dated July 14, 2000)
IgG	Immunoglobulin G
ITT	Intent-to-treat
[redacted]	[redacted]
MCB	Master cell bank
MedDRA	Medical dictionary for regulatory activities
[redacted]	[redacted]
MLt	Mineralization lag time
OS/BS	Osteoid surface/bone surface

OV/BV	Osteoid volume/bone volume
O.Th	Osteoid thickness
PMDA	Pharmaceuticals and Medical Devices Agency
PT	Preferred terms
PTH	Parathyroid hormone
Q2W	Once every 2 weeks
Q4W	Once every 4 weeks
QbD	Quality by design
QOL	Quality of life
RGI-C	Radiographic global impression of change
RSS	Rickets severity score
SE-HPLC	Size exclusion-high pressure liquid chromatography
SMQ	Standardised MedDRA queries
SOC	System organ class
SPR	Surface plasmon resonance
STS	Sit-to-stand (test)
$t_{1/2}$	Elimination half life
TIO	Tumor induced osteomalacia
TmP/GFR	Ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate
WCB	Working cell bank
WOMAC	Western Ontario and McMaster Universities osteoarthritis index
WT	Wild type
XLH	X-linked hypophosphatemic rickets/osteomalacia