These Clinical Study Results are provided for informational purposes only.

This lay summary is a brief summary of the main results from a clinical study. The study listed may include approved and non-approved uses, formulations or treatment regimens. It is not intended to promote any product or indication and is not intended to replace the advice of a health care professional. The results reported in any single clinical trial may not reflect the results obtained across the full clinical development program. Only a physician can determine if a specific product is the appropriate treatment for a particular patient. If you have questions, please consult a health care professional. Before prescribing any product, healthcare professionals should consult the regional approved product labeling for indications and proper use of the product.

Clinical study results

The health effects of burosumab in patients with tumor-induced osteomalacia (TIO)

Thank you!

Thank you to the patients, and their caregivers, who took part in the clinical study for burosumab, also called KRN23, UX023, or Crysvita®. Ultragenyx, the sponsor of this study, is grateful to those who participated and believes it is important to share the results.

By taking part in this study, the patients helped the researchers learn more about using burosumab in people with Tumor-Induced Osteomalacia, also called TIO.

Contents

Study number: **UX023T-CL201**

Why was this study needed?

Researchers designed this study, **UX023T-CL201,** to learn if burosumab could raise phosphorus levels in the blood and lead to healthier bones in patients with Tumor-Induced Osteomalacia (TIO). It was also designed to learn more about the safety of burosumab for these patients.

TIO is a very rare type of osteomalacia caused by tumors that make too much of a protein called **fibroblast growth factor 23**, or **FGF23**. High FGF23 levels cause low levels of phosphorous in the blood and bones. This can lead to muscle weakness, bone pain, and broken bones.

What is osteomalacia?

Osteomalacia is soft or weak bones that break more easily due to an imbalance of phosphorus (a mineral), vitamin D, and calcium in the body. The body's levels of phosphorus, vitamin D, and calcium must be in balance to keep bones healthy.

TIO is also called oncogenic osteomalacia and oncogenic hypophosphatemic osteomalacia.

What is burosumab?

Burosumab, also known as KRN23 or UX023, is a study drug designed to raise phosphorus levels in the blood by blocking FGF23. The researchers thought this could raise phosphorus levels in patients with TIO and lead to healthier bones.

Who was in this study?

This study included **17 patients** from the United States:

- **14 patients had TIO**
- 3 patients had other types of osteomalacia, such as X-linked hypophosphatemia (XLH) or epidermal nevus syndrome (ENS)

The researchers only looked at data from the patients with TIO to answer the main questions in this study.

The patients with TIO were between 33 to 68 years old when they joined this study. Their average age was 57 years old.

All patients with TIO had tumors that could not be removed with surgery. They also stopped taking any phosphorus or vitamin D medicines when they joined this study.

What happened during this study?

Before treatment

The study doctors checked each patient's health and medical records to make sure they could join the study. The study staff looked at a biopsy (sample) from each patient's hip bone.

During treatment with burosumab

The study staff gave each patient burosumab as an injection under the skin every 4 weeks. The study doctor adjusted their dose as needed.

The study staff took blood samples from each patient and checked their health every 2 to 4 weeks.

Each patient had a bone biopsy about 1 year after starting treatment.

After treatment

The study doctor called each patient to check their health about a month and a half after their last dose.

The patients who did not continue to receive burosumab after the study also got another call to check their health around 3 months (12 weeks) after their last dose.

The study started in March 2015 and ended in January 2021. The patients were in the study for up to 6 years.

What were the results from this study?

This is a **summary** of the main results from the group of all patients in this study. Each patient's individual results might be different and are not shown in this summary. If you took part in this study and have questions about your results, please contact the study site.

The results from several studies are needed to decide which treatments work best and are safest. Other studies may give new information or different results. Always talk to a doctor before making any treatment changes.

This study was designed to answer **3 main questions:**

- How many patients with TIO had their phosphorus blood levels go up to a healthy level during the first 24 weeks of receiving burosumab?
- Did patients with TIO have signs of healthier bones after 48 weeks of receiving burosumab?
- What side effects happened during the study?

How many patients with TIO had their phosphorus blood levels go up to a healthy level during the first 24 weeks of receiving burosumab?

Half of the patients with TIO (7 of 14) had their phosphorus blood levels go up to a healthy level during the first 24 weeks of receiving burosumab. The researchers concluded that this was a meaningful change.

To answer this question, the study staff took blood samples from patients before starting treatment and every 2 weeks during the first 24 weeks of treatment. The study staff compared the phosphorus levels in the blood samples to see how the phosphorus levels changed.

Before starting treatment, all 14 patients had phosphorus levels that were too low (not a healthy level).

After receiving burosumab for 24 weeks:

7 out of 14 patients had healthy phosphorus levels

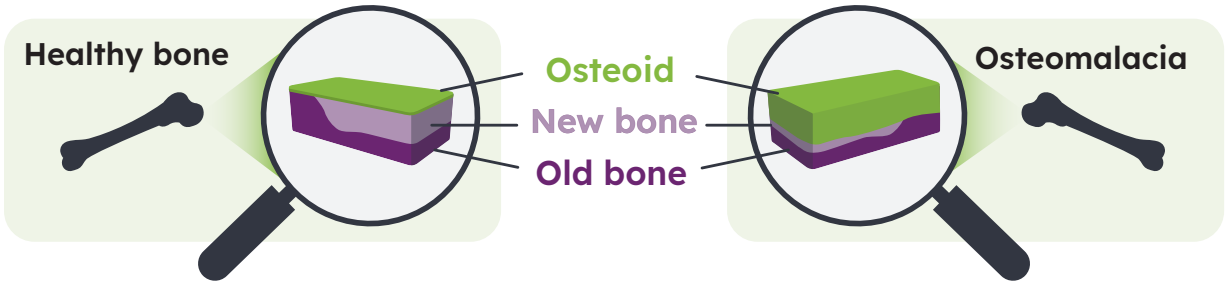
7 out of 14 patients did not have healthy phosphorus levels

Did patients with TIO have signs of healthier bones after 48 weeks of receiving burosumab?

Yes. Some patients had signs of healthier bones after receiving burosumab for 48 weeks.

To see if patients had signs of healthier bones, study staff looked at biopsies (samples) from the patients' hip bones before starting treatment and after 48 weeks of treatment. They checked the samples for osteoid. **Osteoid** is soft area where bone has not yet absorbed enough minerals to harden.

In osteomalacia, **osteoid** is **larger** and hardens **more slowly** than in healthy bone.



Researchers wanted to see if certain osteoid measures went down, which would be signs that the patients' bones were healthier.

Study staff measured the osteoid for:

- Thickness
- Size (volume)
- Length and width (surface area)
- Time to harden (mineralization lag time)

After 48 weeks of treatment, the researchers found that the patients' osteoid:

✓ Was meaningfully thinner

✓ Was meaningfully smaller in size

? Had a slightly smaller length and width
but the researchers couldn't be sure this change was meaningful

? Had a slightly shorter time to harden
but the researchers couldn't be sure this change was meaningful

What side effects happened during this study?

More than half of the patients with TIO in this study (9 of 14) had side effects. Most of these side effects were related to problems at the injection site or unhealthy blood levels of certain nutrients. None of the side effects were considered serious.

What is a side effect?

A **side effect** is an unwanted or unexpected sign or symptom that happens after taking the study treatment.

Side effects may or may not be related to the study treatment, to other drugs taken while in the study, to the patients' medical history, or to any of the tests performed in the study. A lot of research is needed to know if a treatment causes a side effect.

What is a serious side effect?

A side effect is considered **serious** when it:

- Is considered medically important by a doctor
- Requires hospital care
- Causes a disability or birth defect
- Is life-threatening
- Causes death

This is a summary of the side effects that happened during the study that the doctors thought might be related to the study treatment.

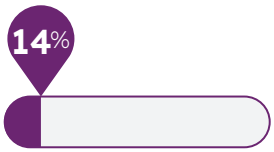
What serious side effects did patients with TIO have during this study?

No patients had serious side effects during this study. No deaths related to burosumab happened during this study.

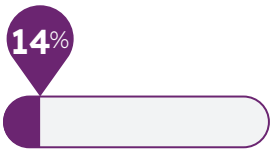
What other side effects did patients with TIO have during this study?

Overall, 64% of patients with TIO (9 of 14) had side effects during this study.

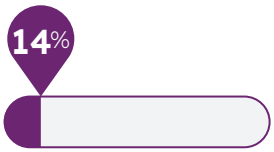
Below are the side effects that happened in **at least 10% of all the patients in this study** (2 or more patients). There were other side effects that happened in fewer patients.



Blood phosphorus levels that were too high
(Hyperphosphatemia)
2 of 14 patients



Blood vitamin D levels that were too low
(Vitamin D deficiency)
2 of 14 patients



Rash, pain, or swelling at the site of the injection
(Injection site reaction)
2 of 14 patients

How has this study helped patients and researchers?

Overall, half of the patients with TIO had their phosphorus blood levels go up to a healthy level during the first 24 weeks of receiving burosumab. Some patients also had signs of healthier bones after 48 weeks of receiving burosumab. Researchers found no new safety concerns for burosumab when given to patients with TIO. Please talk with your doctor if you have any questions about burosumab.

These results are for the UX023T-CL201 study only. There are ongoing studies on burosumab. Other studies may have new or different results. Always talk to a doctor before making any treatment changes.

Where can I learn more about this study?

You can find more information about this study, including a report with the study's results, on this website:

- https://clinicaltrials.gov/ct2/show/NCT02304367

Official Study Title: A Phase 2 Open-label Trial to Assess the Efficacy and Safety of KRN23, an Antibody to FGF23, in Subjects with Tumor-induced Osteomalacia (TIO) or Epidermal Nevus Syndrome (ENS)-associated Osteomalacia

National Clinical Trial number: NCT02304367

If you have questions about the results, please speak with a doctor or staff at the study site.

Thank you!

At Ultragenyx, our focus is developing medicines for people who live with rare and ultra-rare diseases. But it takes more than scientific knowledge and research to develop medicines. Your involvement is essential and ensures that the research process moves forward. Thank you for your participation in this study and commitment to research.

Ultragenyx is a biopharmaceutical company committed to bringing patients products for the treatment of rare and ultra-rare diseases, with a focus on serious, debilitating genetic diseases.

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