What is FGF23-related hypophosphatemic rickets and osteomalacia?

**FGF23-related hypophosphatemic rickets and osteomalacia**

### Disease characteristics
- A type of rickets/osteomalacia caused by excessive actions of the hormone FGF23, which lowers blood phosphate levels and inhibits bone calcification.
- A rare and intractable disease, it is associated with growth impairment and bone deformity in children; in adults, symptoms include bone pain, proneness to fracture and muscle weakness leading to lack of strength.

### Causes and potential patient population
- FGF23-related hypophosphatemic rickets and osteomalacia is a “designated intractable disease in Japan”. Among its causes, the incidence rate of inherited X-linked hypophosphatemia (XLH) is estimated at 1 in 20,000 people.
- In XLH, genetic factors on the X chromosome cause excessive excretion of systemic phosphate in the urine, resulting in chronically low blood phosphate levels.
- Phosphate is a mineral required for forming healthy bones and teeth as well as for maintaining the body's energy levels and muscle function and is essential to human life.

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Healthy subjects and XLH patients have different FGF23 levels

Yamazaki, et al. JCEM 2002
Our goal was to elucidate the biological factors involved in the regulation of bone metabolism and apply them to drug discovery.

- Kirin Brewery's former Pharmaceutical Development Laboratory (at that time) was researching bone metabolism.
- Development was prompted by a focus on phosphate due to concurrent research in the key area of nephrology.
- Phosphate is the second most abundant mineral in the body after calcium, and is a major component of bones and teeth.
- Compared to calcium, however, research into phosphate regulation mechanisms lagged behind globally at the time. Kirin's researchers saw an opportunity to help patients suffering from related diseases and began their studies.
• In 2000, based on research into the pathogenesis of hypophosphatemia, we made the unprecedented discovery that FGF (fibroblast growth factor) 23 plays a central role in regulating blood phosphate levels.

• FGF23 is a humoral factor (hormone) that lowers blood phosphate produced by osteocytes. Suppression of FGF23 raises vitamin D and reduces phosphate excretion from the kidneys. We hypothesized that this may help treat XLH, and continued our research.

• The problem was how to suppress FGF23. By utilizing Kirin's human antibody production technology, we were able to create KRN23, an anti-FGF23 antibody suitable for the therapeutic purpose of suppressing FGF23.
Discovery of anti-FGF23 antibodies

The road to discovery of anti-FGF23 antibodies

1998 Joint research with Dr. Seiji Fukumoto, University of Tokyo Hospital (at that time)
*Presently Fujii Memorial Institute of Medical Center, Tokushima University

Resected tumors were found to be overproducing an unknown phosphate-lowering hormone

Unknown phosphate-lowering hormone identified from resected tumors — toward discovery
Expanding the use of anti-FGF23 antibody

To contribute patients around the world

<table>
<thead>
<tr>
<th></th>
<th>Japan, USA, Canada, UK, eight EU countries*, Israel, UAE, Norway, Bahrain, Oman</th>
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<tbody>
<tr>
<td><strong>Launched</strong></td>
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<td><strong>Approved</strong></td>
<td>18 EU countries other than the above, Iceland, Liechtenstein, Switzerland and Hong Kong</td>
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<tr>
<td><strong>Under Review</strong></td>
<td>China, Taiwan, Singapore, Kuwait and Saudi Arabia</td>
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As of June 30, 2020*Germany, Netherlands, Luxembourg, Slovakia, Sweden, Czech Republic, Denmark, Italy

<table>
<thead>
<tr>
<th>Year</th>
<th>Net sales</th>
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<tr>
<td>2018</td>
<td>7.7 billion yen (overseas)</td>
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<tr>
<td>2019</td>
<td>32.5 billion yen (overseas)</td>
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<tr>
<td>2020 forecast</td>
<td>51.1 billion yen (overseas) 3.5 yen (in Japan)</td>
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