Plain Language Summary of Publication

Journal of Comparative Effectiveness Research

Effectiveness and safety of asfotase alfa for people with hypophosphatasia: a plain language summary of three studies

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First draft submitted: 2 December 2024; Accepted for publication: 24 February 2025; Published online: 20 March 2025

Summary

What is this summary about?

Hypophosphatasia (HPP for short) is a rare inherited condition that can present at any stage of life, with symptoms typically being more severe in cases that manifest earlier, such as during infancy or childhood. This article summarizes three published studies that looked at the safety and effectiveness of asfotase alfa for people with HPP. The aim of this article is to present the findings of three studies clearly and engagingly to make them accessible to readers without a scientific background.

The first study (called study 1) discussed in this article looked at how safe and effective asfotase alfa was for children with life-threatening HPP. The second study (called study 2) looked at how safe and effective asfotase alfa was for children or adolescents who had showed the first signs of HPP at birth or in childhood. They received treatment in clinical practice in Japan, rather than in a clinical research study. The third study (called study 3) looked at how safe and effective asfotase alfa was for adults with HPP who had showed the first signs of the condition in childhood. They received treatment in clinical practice, rather than in a clinical research study.

What were the results?

In study 1, asfotase alfa improved bone health, the ability to breathe, and growth in children with life-threatening HPP. The researchers saw these benefits over 6 years of follow-up by HPP care teams. The treatment was generally well-tolerated.

In study 2, asfotase alfa relieved symptoms such as pain, improved growth, and improved the ability to breathe in children and adolescents with HPP in Japan. The treatment was generally well-tolerated, with no serious side effects. Some participants had mild reactions at injection sites.

In study 3, asfotase alfa improved physical function and quality of life for adults with HPP. People were able to walk further and faster and had improved grip strength. The researchers saw these benefits as early as 3 months, and they continued over 2 years. The treatment was well-tolerated. Some people had mild reactions at injection sites.

What do the results of the studies mean?

The combined results from these studies indicate that asfotase alfa is effective and safe to treat people with HPP of different ages and levels of symptom severity. Asfotase alfa improves bone health, mobility, growth, and breathing ability, and relieves pain. Treatment can improve quality of life for people with HPP. The findings from these studies support the continued use and further development of asfotase alfa as a treatment for people with HPP.

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Clinical practice: The routine way doctors and healthcare professionals diagnose and treat patients.

Injection-site reaction: Redness, swelling, or discomfort where a medicine is injected into the skin.

Quality of life (QoL): A measure of how a person's health condition affects their daily life, including their physical, emotional, and social well-being.

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How to say (double click on the sound icon to play the sound)

Alkaline phosphatase : AL-kuh-line FO-sfuh-tays
***ALPL* gene:** A-L-P-L jeen
Antibodies: AN-tee-bah-dees
Asfotase alfa: AZ-fo-tase AL-fa
Bone mineralization: bohn MIN-uh-ruh-li-ZAY-shun
Craniosynostosis: kray-nee-oh-sin-oh-STO-sis
Genetic counseling: juh-NET-ik KOWN-suh-ling
Inorganic pyrophosphate: in-or-GAN-ik pie-ro-FOS-fate
Injection-site reaction: in-JEK-shun site ree-AK-shun
Lipodystrophy: lie-poh-DIS-troh-fee
Osteomalacia: os-tee-oh-muh-LAY-shuh
Phosphoethanolamine: fos-fo-ETH-uh-nol-a-meen
Pseudofracture: soo-do-FRAK-chur
Pyridoxal 5'-Phosphate : pie-rih-DOX-uhl five-FOS-fate
Respiratory support: RES-pih-ruh-tor-ee suh-PORT
RGI-C scores: R-G-I-C skorz
Scoliosis: sko-lee-OH-sis
Seizures: SEE-zhurz
Skeletal abnormalities: SKEL-uh-tuhl ab-nor-MAL-ih-tees

Who is this article for?

This article may be useful for:

- People with HPP, their families, or caregivers.
- Patient associations or other organizations helping people with HPP.
- Healthcare providers (such as physicians and nurses) who treat people with HPP.
- Healthcare providers or policymakers who draft HPP management recommendations.
- Anyone who wants to learn more about HPP.

What is hypophosphatasia?

- Hypophosphatasia (HPP for short) is a rare inherited condition that affects people of all ages. People living with HPP can have a wide range of symptoms which negatively impact their quality of life.
- Severe forms of HPP have an estimated prevalence of 1 in 300,000 births in Europe, but milder cases may be more common and often go undiagnosed.
- While there is no cure for HPP, early diagnosis and appropriate treatment are crucial to address the complex challenges related to this condition.
- HPP is caused by changes in a gene called *ALPL*. Having this gene change makes it difficult for the body to produce enough normally functioning alkaline phosphatase enzyme (ALP for short).
- ALP is essential for body functions including the process of adding minerals to bones and teeth to make them strong.

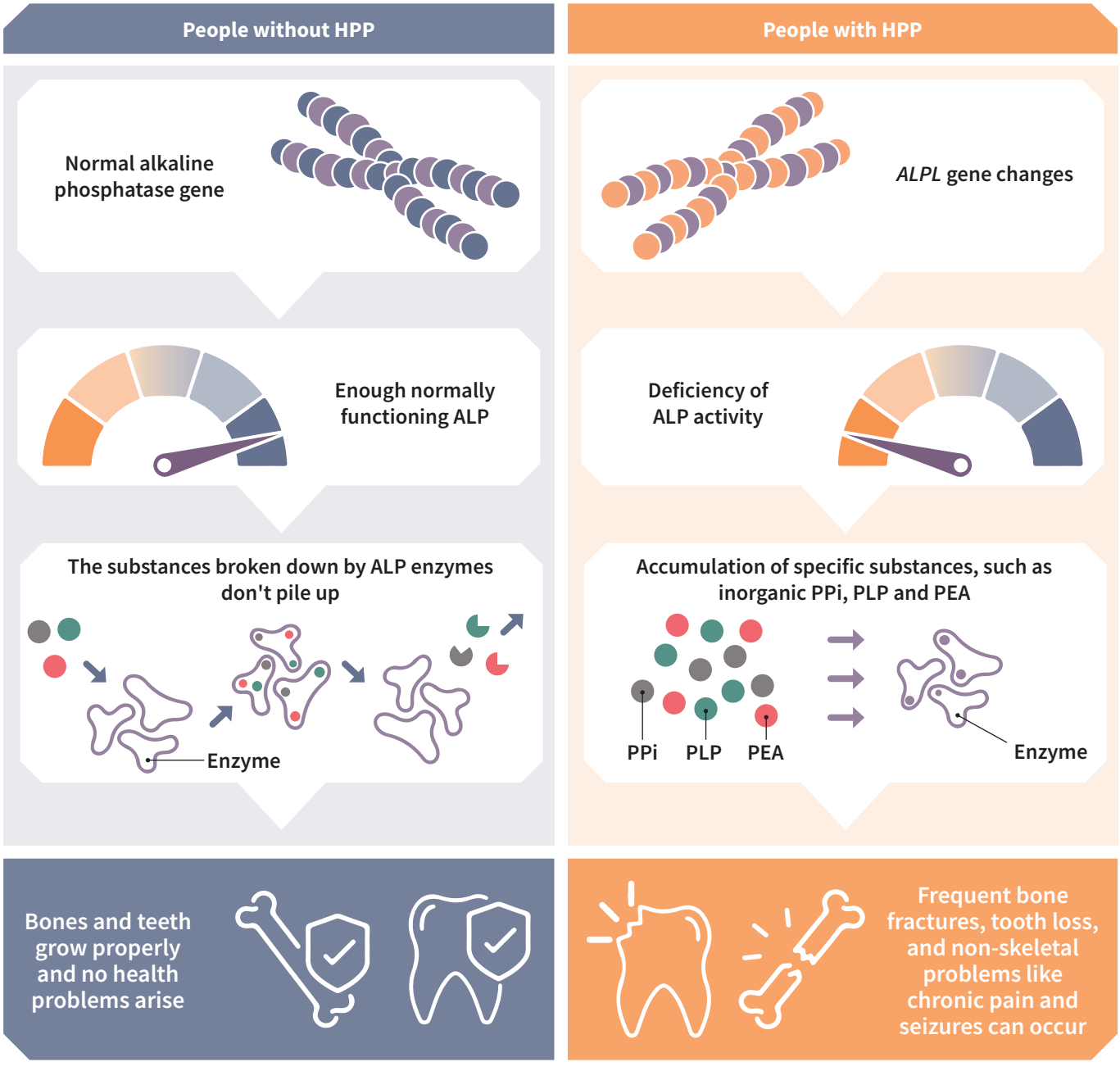
ALP (alkaline phosphatase): An enzyme that helps bones and teeth grow strong. People with HPP have low ALP levels, which can cause weak bones.
***ALPL* gene:** The gene that provides instructions for making the ALP enzyme. Changes (variants) in this gene cause HPP by reducing ALP enzyme activity.
Enzyme: A special protein in the body that helps chemical reactions happen, like breaking down substances or building new ones.
Gene: A part of DNA that carries instructions for how the body works. Changes in the *ALPL* gene cause HPP by reducing ALP enzyme activity.
Seizures: Sudden bursts of abnormal electrical activity in the brain, which can cause shaking, confusion, or loss of awareness. In HPP, seizures may occur due to vitamin B6 not working properly.

- ALP deficiency means that specific substances build up in the body. These include:

- Inorganic pyrophosphate (PPi for short). Build-up of PPi stops the process of adding minerals to bones and teeth. This can lead to problems with bone structure, dental issues, and breathing problems caused by changes to the shape of the chest.

- Pyridoxal 5'-Phosphate (PLP for short). PLP is a form of vitamin B6 that needs the ALP enzyme to work effectively in the body, particularly in the brain. Build-up PLP can cause seizures that can be treated with vitamin B6 supplements.

- Phosphoethanolamine (PEA for short). PEA is a natural substance normally processed by ALP. The effect of PEA building up in the body is not yet understood by researchers.



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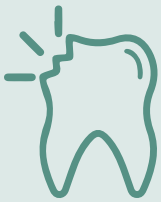
What are the symptoms of HPP?

- Symptoms can vary widely depending on the person's age. The most common symptoms are:

Bone problems

- Bones may be soft and weak, leading to changes in bone structure and frequent fractures.



Dental issues

- Premature loss of baby teeth is common, often without the root breaking down as it normally would.

Breathing problems

- Some people have changes to the structure of the chest wall, leading to breathing difficulties.

Seizures that can be treated with vitamin B6

- These may be the first symptom in infants. When seizures appear early, they may indicate more severe health problems that can affect overall life expectancy.

Musculoskeletal problems

- Such as long-term pain, muscle weakness, and fatigue.

Fracture:
A broken bone. People with HPP are more likely to have fractures due to weak bones.

Seizures:
Sudden bursts of abnormal electrical activity in the brain, which can cause shaking, confusion, or loss of awareness. In HPP, seizures may occur due to vitamin B6 not working properly.

Skeletal abnormalities:
Problems with bone shape or strength, common in HPP, which can lead to fractures, soft bones, or deformities.

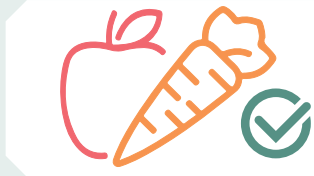
Muscle weakness:
A symptom of HPP where muscles feel weaker than normal, making it harder to move or do daily activities.

Fatigue:
A common symptom of HPP that causes extreme tiredness and low energy.

Lifestyle changes

- Lifestyle can also play an important role in managing HPP.

- For example, a balanced diet that includes calcium-rich foods such as dairy products, leafy greens, and fortified alternatives, along with sources of vitamin D like fatty fish, eggs, and fortified cereals, supports bone health.



- Additionally, appropriate low-impact exercises, such as swimming, walking, or resistance training with light weights, can help strengthen muscles and improve mobility.

- However, it's important to avoid high-impact activities or those with a high risk of falls, as they may increase the risk of fractures.

Common HPP symptoms based on the persons's age

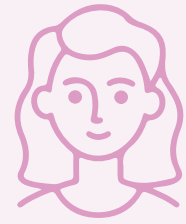
Infants

- Softening and weakening of bones (rickets), though not always present.
- A sideways curve in the spine (scoliosis).
- High calcium levels in the blood.
- Problems with growth and development.
- Early fusion of skull bones (craniosynostosis), leading to increased pressure in the brain.
- Breathing problems: Weak or soft ribs and changes in chest shape can make it hard for infants to breathe, sometimes requiring breathing support, such as extra oxygen or a machine to help them breathe.
- Seizures that can be treated with vitamin B6.
- Risk of early death: Due to respiratory issues and vitamin B6-responsive seizures.

Children (<18 years of age)

- Loss of baby teeth before age 5.
- Waddling gait and delayed walking: Due to irregularities in bone and joint development.
- Softening and weakening of bones (rickets) that can cause short stature, curved legs, and larger-than-normal joints, though it does not always appear.
- High calcium and/or phosphate levels in the blood due to problems with bone mineralization.
- Bone pain and joint discomfort: Including stiffness, swelling, and muscle weakness.
- Most children are of normal height, though usually shorter than expected for their family background.

Adults (≥18 years of age)



- Fractures and pseudofractures (areas of weakened bone that resemble fractures): Especially in the feet and thigh bone. These often heal poorly and may need to be treated with surgery.
- Softening and weakening of the bones due to lack of minerals (osteomalacia).
- Musculoskeletal symptoms: Long-term pain, muscle weakness, and fatigue with significant impact on quality of life.
- Problems with teeth: such as early tooth loss, fragile or cracked teeth, and increased risk of cavities.
- Reduced mobility: Problems with walking and daily activities, often requiring assistive devices like wheelchairs.

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Rickets: A condition in children where bones become soft and weak due to poor mineralization, similar to osteomalacia in adults.

Scoliosis: A condition where the spine curves sideways, which can happen in some people with HPP.

Growth delay: A slower-than-normal increase in height and weight, often seen in children with HPP.

Craniosynostosis: A condition where the bones of a baby's skull join too early, which can cause changes in head shape and pressure in the brain.

Bone mineralization: The process of adding minerals to bones to make them strong. In HPP, this process is disrupted, leading to weak bones.

Pseudofracture: A small, incomplete break in a bone that can look like a fracture but develops differently.

Osteomalacia: A condition in adults where bones become soft and weak due to poor mineralization, often causing pain and fractures.

What medications or treatments are commonly used for HPP?

Enzyme replacement therapy

- The main treatment for HPP is to replace the deficient ALP enzyme. The only approved treatment for HPP is called asfotase alfa.
  - People receive asfotase alfa as injections under the skin, often several times per week.

Supportive care

- In addition to enzyme replacement therapy, supportive care is crucial in managing HPP, not only for patients but also for their families, who play a key role in daily care, treatment adherence, and emotional support.
  - Pain relief medications like acetaminophen (paracetamol) and ibuprofen can help manage bone pain. For more severe pain, doctors may consider stronger options like opioids or muscle relaxants, but these must be used with caution and under medical supervision due to possible side effects. Physical therapy can help manage bone pain and muscle weakness.
  - Regular dental care is important to address tooth loss and other dental issues.
  - Infants with trouble breathing may need extra oxygen or a machine to help them breathe. These respiratory issues are not common in adults with HPP, as their bones and respiratory muscles are fully developed.
  - Management of seizures, which may be prevented by and treated with vitamin B6.
  - Optimizing calcium and vitamin D levels to help support bone health.
  - Surgery for issues such as craniosynostosis, scoliosis, and fracture.
  - Genetic counseling can help families understand the risk of passing the condition to their children. If the condition is found early through genetic testing, doctors can start treatment sooner if needed.

Approved treatment: A medicine or therapy officially approved by health authorities for treating a condition, like asfotase alfa for HPP.

Pain management: Different ways to reduce pain, such as medications, physical therapy, or lifestyle changes.

Genetic counseling: A service that helps families understand how genetic conditions like HPP are inherited and what their options are.

Lifestyle changes

- Lifestyle can also play an important role in managing HPP.
- For example, a balanced diet that includes calcium-rich foods such as dairy products, leafy greens, and fortified alternatives, along with sources of vitamin D like fatty fish, eggs, and fortified cereals, supports bone health.
- Additionally, appropriate low-impact exercises, such as swimming, walking, or resistance training with light weights, can help strengthen muscles and improve mobility.
- However, it's important to avoid high-impact activities or those with a high risk of falls, as they may increase the risk of fractures.

Living with HPP can be challenging, but with the right care and support, people with this condition can lead healthier and more active lives. However, diagnosing HPP can be difficult because its symptoms vary widely and may be mistaken for other conditions. Raising awareness among healthcare providers and the general public is important to ensure earlier diagnosis, which can help prevent complications and improve outcomes.

Which studies looked at asfotase alfa for the treatment of people with HPP?

Three key studies looked at asfotase alfa for the treatment of people with HPP.

Study 1

- The first study looked at how safe and effective asfotase alfa was for children age 5 years or less with life-threatening HPP.
- The children took part in a clinical research study, meaning they were involved in a structured investigation where researchers collect information to better understand how a new treatment works.

Study 2

- The second study looked at how safe and effective asfotase alfa was for children or adolescents who had showed the first signs of HPP at birth or in childhood.
- They received treatment in clinical practice in Japan, rather than in a clinical research study.

Study 3

- The third study looked at how safe and effective asfotase alfa was for adults with HPP who had showed the first signs of the condition in childhood.
- They received treatment in clinical practice, rather than in a clinical research study.

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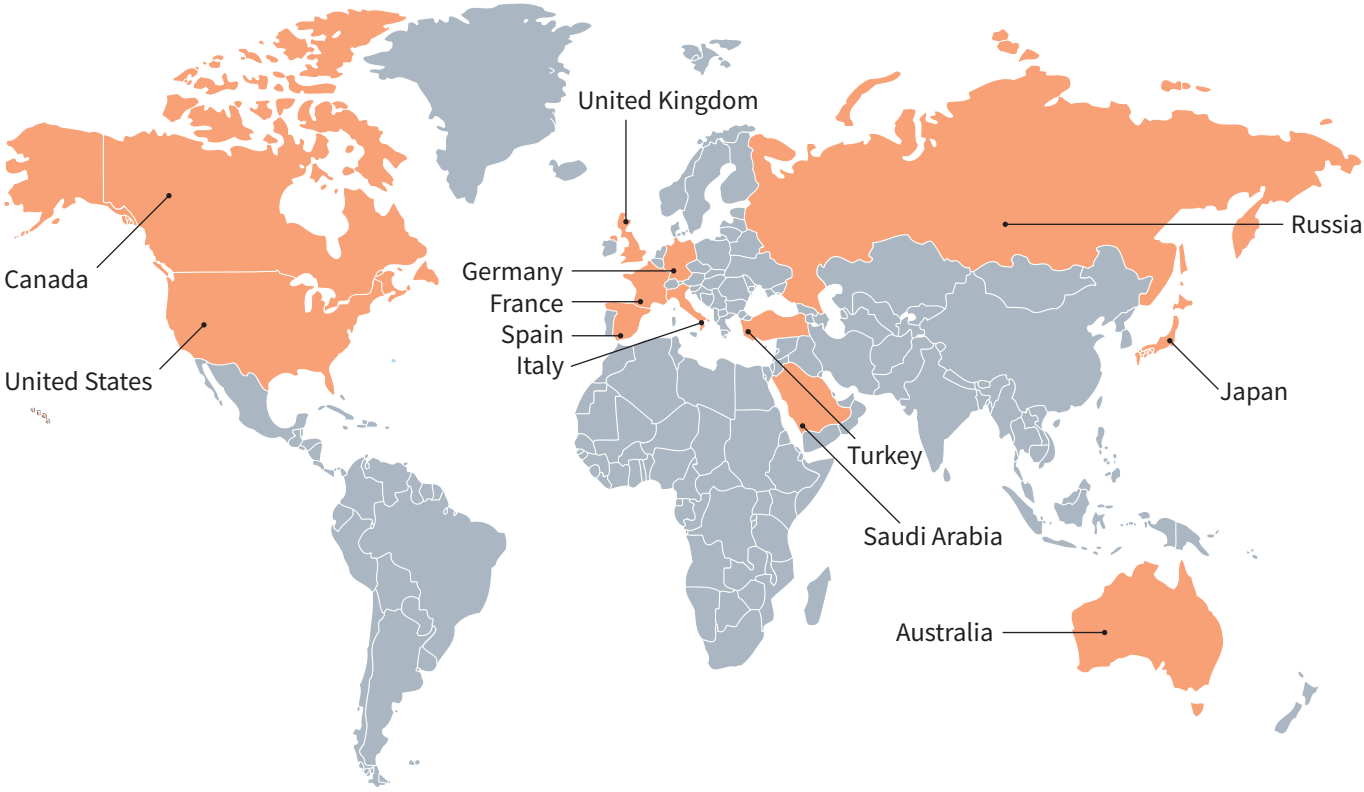
What were the findings of Study 1 performed in children with life-threatening HPP?

- Study 1 looked at how safe and effective long-term treatment with asfotase alfa was for infants and children aged 5 years or younger with life-threatening HPP.

How was the study carried out?

- The study was done from July 2010 to September 2016.
- 69 children from 22 sites in 12 countries took part.
  - All the children were under 5 years old and had life-threatening, rapidly progressing HPP symptoms that started before 6 months of age.

Which countries participated in the study?



How was asfotase alfa administered?

- The children received injections of asfotase alfa under the skin, either:
  - Three times a week, with the dose based on body weight (2 milligrams for each kilogram of body weight per dose).
  - Six times a week, with the dose based on body weight (1 milligram for each kilogram of body weight per dose).

Dose: 2 mg × 1 kg of body weight

Dose: 1 mg × 1 kg of body weight

What did the researchers look at?

- To find out how effective and safe asfotase alfa was, the researchers looked at:

Improvement in bone health

- The study used X-rays to measure improvements in the children's bones, specifically looking at a score called the Radiographic Global Impression of Change (RGI-C).
- This score ranges from -3 (severe worsening) to +3 (complete healing).
- Children were considered to be responders if they achieved an RGI-C score greater than or equal to +2.

Respiratory status

- The researchers checked whether children required assistance with breathing, such as using a ventilator or oxygen, and monitored the improvement in their breathing over time.

Growth measurements

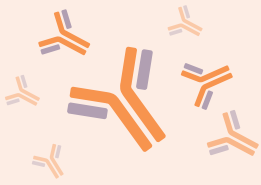
- The researchers tracked changes in the height, weight, and head size of the children.

Survival rates

- Survival rates indicate the percentage of children who are still alive at the end of the study.

Biochemical markers

- The researchers measured ALP levels and other substances in the blood, like enzymes and vitamin B6, which help keep bones healthy.



Antibodies against the treatment (anti-asfotase antibody levels)

- The researchers checked if the children's bodies were producing antibodies against the treatment.

Side effects

- The researchers recorded any negative reactions or issues the children experienced during treatment, especially at the injection site.

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RGI-C scores: A tool used by doctors to measure improvements in bone health in people receiving treatment for HPP.

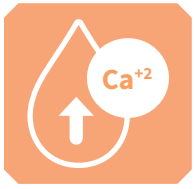
Respiratory support: Treatments like oxygen therapy or ventilators that help people with breathing difficulties, which can occur in severe cases of HPP.

What were the characteristics of the children who took part?

36 girls **33** boys

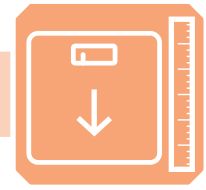
- The average age of the children was 18 months.
- They had shown the first signs of HPP at around 1 month of age.

- The children had experienced a range of different medical problems related HPP:



61 out of 69 children (88%) had too much calcium in their blood

60 out of 69 children (87%) had trouble gaining weight, growing properly , or eating and swallowing

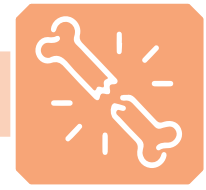


58 out of 69 children (84%) had changes in their chest shape

46 out of 69 children (67%) had breathing problems, including serious cases where they needed help to breathe

37 out of 69 children (54%) had calcium buildup in their kidneys, which could affect kidney function

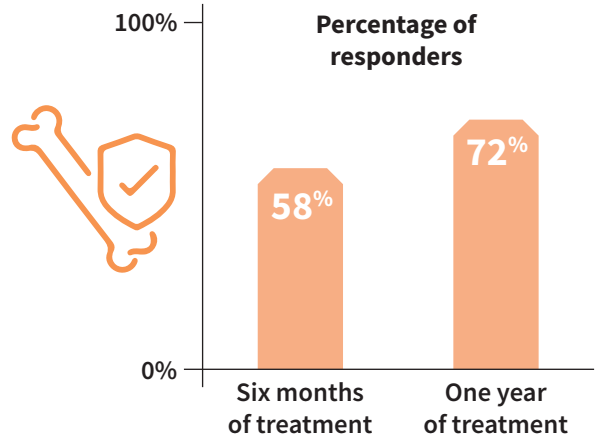
21 out of 69 children (30%) had bones that broke easily or healed slowly

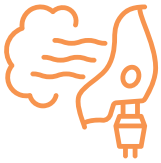


17 out of 69 children (25%) had seizures

What were the main results?

- **Improvement in bone health:**
  - Most children had significant improvement in their bone mineralization.
  - After 6 months of treatment, over half of the children (58%) had responded with RGI-C scores of +2 or higher. This showed substantial bone healing.
  - After 1 year of treatment, nearly three-quarters of the children (72%) had responded with RGI-C scores of +2 or higher. This showed substantial bone healing in most of the children.



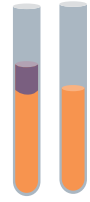


- **Breathing function:**
  - The treatment helped numerous children breathe better independently.
  - Out of the 45 children who did not need respiratory support at the start of the study, the majority (43 children; 96%) remained free of respiratory support at the end of the study.
  - Out of the 24 children who needed respiratory support at the start of the study, around half (11 children, 46%) no longer needed support at the end of the study.

- **Growth measurements:**
  - The researchers saw significant increases in children's height, weight, and head circumference during the study. This showed that their growth patterns had improved.

- **Survival rates:**
  - Most children who received the treatment survived and continued to benefit from the treatment.
  - Among all 69 children, researchers estimated that 80% were still alive after 6 years. This estimate is based on a method that accounts for children who did not stay in the study for the full 6 years. In comparison, historical data suggest that untreated infants with severe forms of HPP have significantly lower chances of survival, often below 50%.

- **Biochemical markers**
  - Children's level of ALP in the blood significantly increased.
    - Before starting treatment, the average ALP level was approximately 20 U/L. After 3 weeks of treatment, it rose to about 3761 U/L and continued to increase to about 6742 U/L by the end of the first year of the study.
    - The researchers expected to see this rise. It suggests that the treatment was effectively providing the deficient enzyme.
  - PPi and PLP levels reduced to normal by 6 weeks of treatment and remained within the normal range through year 5 of the study.



- **Antibodies against the treatment (anti-asfotase alfa antibodies):**
  - 88% of the children developed anti-asfotase alfa antibodies.
  - Having antibodies was not related to the treatment becoming less effective, or to being more likely to have side effects.

Antibodies against the treatment (anti-asfotase alfa antibodies): Proteins produced by the immune system in response to asfotase alfa. These antibodies may develop in some people receiving treatment, but they do not always affect how well the treatment works.

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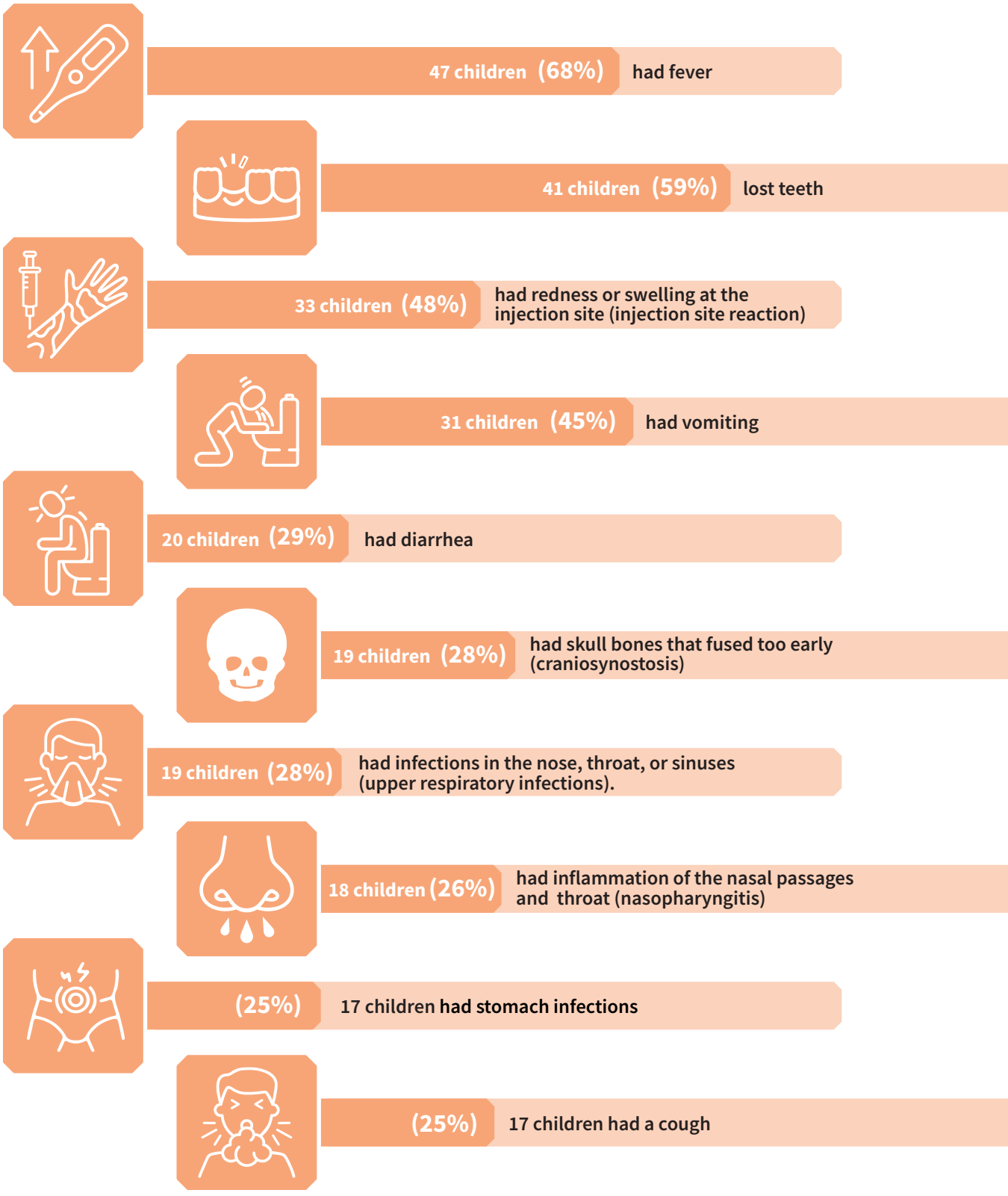
What side effects did people experience in the study?

- Most common side effects:



(23%) 16 children had respiratory infections

(23%) 16 children had constipation

(20%) 14 children had pneumonia

- Most side effects were mild (70%) or moderate (24%) in severity. The researchers reported that 79% of side effects were unrelated to the study treatment.

Side effects

70% mild

24% moderate

79% of side effects were unrelated to the study treatment

9% of participants had serious side effects related to the treatment

- 9% of participants experienced serious side effects that the researchers reported were related to the treatment.
- The majority (64%) of serious treatment-related side effects were swelling, redness, or other reactions at the injection site, or general reactions after the injection.

Side effects are grouped by how much they affect daily life

- **Mild:** Small issues that you may notice but don't stop you from doing normal activities (e.g., slight redness where the injection was given).
- **Moderate:** Can be uncomfortable and might make daily activities harder, but usually don't need medical help (e.g., feeling tired or having mild pain).
- **Severe:** Serious issues that can make daily life difficult and may need medical attention (e.g., a strong allergic reaction or severe pain).

What do the results of this study mean?

Overall, the study supports the use of asfotase alfa as a safe and effective long-term treatment option for young children with life-threatening HPP. Asfotase alfa improved thee bone health, growth, respiratory function, and chances of survival for the children in the study.

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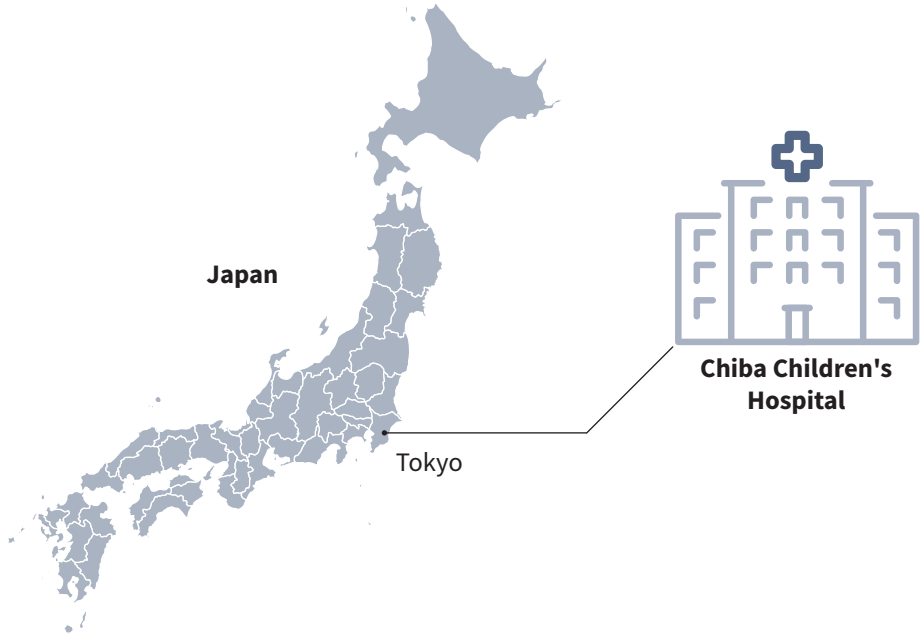
What were the findings Study 2 performed in children with HPP in clinical practice?

- Study 2 looked at how safe and effective asfotase alfa was for children with HPP receiving treatment at Chiba Children's Hospital in Japan.



How was the study carried out?

- 10 children and adolescents (6 boys and 4 girls) took part in the study. They had showed the first signs of HPP before they were born or in childhood.

How was asfotase alfa administered?

- The children received injections of asfotase alfa under the skin, either:
  - Three times a week, with the dose based on body weight (2 milligrams for each kilogram of body weight per dose).
  - Six times a week, with the dose based on body weight (1 milligrams for each kilogram of body weight per dose).

3 times a week

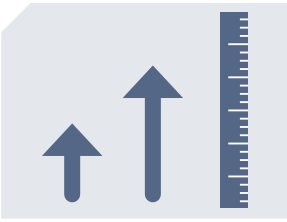
Dose: 2 mg × 1 kg of body weight

6 times a week

Dose: 1 mg × 1 kg of body weight

What did the researchers look at?

- The researchers collected information about the children's health to assess the treatment's impact. Indicators measured included:

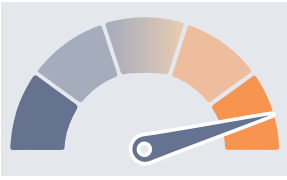


Growth measurements

- General physical growth and development.

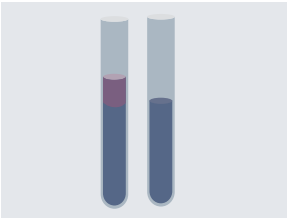
Bone health

- Checking how strong the bones are (bone density) and looking for any bone problems that could happen with the condition.



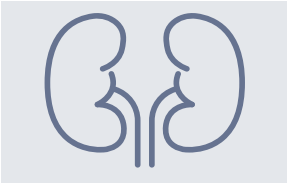
Pain levels

- Assessment of limb pain and discomfort.



Biochemical data

- Testing blood and urine to measure specific substances that help doctors understand how the body is working.



Kidney health

- Monitoring using ultrasound (a medical imaging technique that uses sound waves to create pictures of the kidneys, helping doctors check their size, shape, and function).

Walking ability assessment

- Researchers used the 6-minute walk test to track mobility and response to treatment.

- Researchers also collected information about potential side effects from the treatment.
- During the study, any side effects were carefully recorded. They were grouped as mild, moderate, or severe and reviewed by the research team. This information helped researchers understand how safe the treatment was and how to better care for participants.

6-minute walk test: A simple test that measures how far a person can walk in six minutes. It helps assess physical fitness and mobility.

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What were the main results?

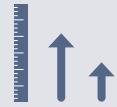
- The results showed significant improvements in clinical symptoms for all participants. This included reduced pain, improved growth, and better physical abilities.
- The table below offers a summary of how participants reacted to treatment on a case-by-case basis. Each individual case outlines the participants' initial symptoms, when they began treatment, and the improvements observed over time.

Improvement in bone health

1

Sex	Age at first signs of HPP	Age at treatment start	Age at last follow-up
 Male	2 years	5 years	7 years

Outcome


Height increase
104 cm to 117 cm

Walk test improved
350 m to 400 m

This boy experienced leg pain at 2 years old and early tooth loss and arm pain at 4 years old. After receiving asfotase alfa, his leg pain improved, and the rate of early tooth loss decreased. His height increased from 104 cm to 117 cm two years after starting the treatment. His 6 minute-walk test improved from 350 m to 400 m. The forearm bones returned to their normal shape. Before treatment, the ends were curved inward and widened, but these changes disappeared with treatment. Mild loss of fat tissue was seen where the treatment was injected.

2

Sex	Age at first signs of HPP	Age at treatment start	Age at last follow-up
 Female	6 months	10 years 1 month	12 years

Outcome

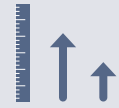
Walk test improved
380 m to 433 m

Diagnosed with poor weight gain and bone abnormalities at 6 months old. Asfotase alfa helped her manage pain and improved her school attendance. Her 6 minute-walk test increased from 380 m to 433 m.

3

Sex	Age at first signs of HPP	Age at treatment start	Age at last follow-up
 Male	1 year 4 months	1 year 5 months	3 years 2 months

Outcome


Height increase
74 cm to 87 cm


Bone health
improved

Experienced early tooth loss when he was 1 year and 4 months. After 1 year and 7 months of asfotase alfa treatment, his height increased from 74 cm to 87 cm and bone abnormalities improved. Mild loss of fat tissue was seen where the treatment was injected.

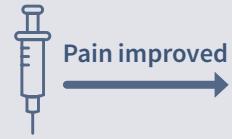
4

Sex	Age at first signs of HPP	Age at treatment start	Age at last follow-up
 Male	9 years 10 months	11 years 5 months	12 years 2 months

Outcome


Pain improved

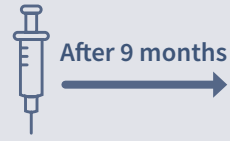

At 9 years old, he started experiencing pain in his right knee and hip joint. Asfotase alfa alleviated his pain. Mild loss of fat tissue was seen where the treatment was injected.

	Sex	Age at first signs of HPP	Age at treatment start	Age at last follow-up	Outcome
5	 Male	7 years	10 years 4 months	12 years 7 months	 Height increase 127 cm to 142 cm  Pain improved

Had shorter-than-average height and bone or joint problems that affected movement. After 2 years and 3 months of treatment with asfotase alfa, his height increased from 127 cm to 142 cm, and his pain improved. He had unusual fat build-up and lost some fat tissue, with skin redness where the treatment was injected.

	Sex	Age at first signs of HPP	Age at treatment start	Age at last follow-up	Outcome
6	 Female	10 years	17 years 1 month	18 years 7 months	 6 min Walk test improved 356 m to 410 m

Suffered from knee pain and scoliosis. Asfotase alfa treatment was started at 16 years old. The treatment reduced her pain and fatigue and improved her 6-minute walking distance from 356 m to 410 m. Mild loss of fat tissue was seen where the treatment was injected. (Sibling of participant 5).

	Sex	Age at first signs of HPP	Age at treatment start	Age at last follow-up	Outcome
7	 Male	4 years 2 months	4 years 3 months	5 years 2 months	 After 9 months  Any premature loss of teeth  Bone health improved

Lost a tooth early. Nine months after beginning asfotase alfa, he had not experienced any further premature loss of teeth, and his bone health improved. He had mild redness at injection sites.

	Sex	Age at first signs of HPP	Age at treatment start	Age at last follow-up	Outcome
8	 Male	At birth	16 years 3 months	21 years 1 month	 6 min Walk test improved 463 m to 560 m

At birth, he had unequal limb lengths. At 15 years of age, he had calcium build-up in both kidneys asfotase alfa was started at 15 years old. The treatment improved his 6-minute walking distance from 463 m to 560 m and cleared the calcium build-up in his kidneys. He had unusual fat build-up and lost some fat tissue, with skin redness where the treatment was injected.

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9	Sex	Age at first signs of HPP	Age at treatment start	Age at last follow-up	Outcome
	Female	In utero	1: 6 years 3 months 2: 4 years 5 months	9 years 4 months	Height increase 103 cm to 119 cm After 1 year and 4 months still had a small amount of calcium build-up

An ultrasound before birth showed that both thigh bones (femurs) had an abnormal shape. She started asfotase alfa treatment at 4 years old to help with her short height but stopped after a week because the injections were painful. Treatment started again at age 6 due to concerns about her height and calcium build-up in her kidneys. Over time, her fatigue gradually improved. After 1 year and 4 months of treatment, she still had a small amount of calcium build-up in her kidneys. Her height had increased from 103 cm to 119 cm at age 3 years and 1 month. She had unusual fat build-up and lost some fat tissue, with skin redness where the treatment was injected.

10	Sex	Age at first signs of HPP	Age at treatment start	Age at last follow-up	Outcome
	Female	In utero	At birth	4 years 2 months	Height increase 35 cm to 73 cm After 2 years and 4 months

Doctors saw that she had short limbs before birth, and she was born with severe breathing problems. Asfotase alfa treatment helped improve her breathing. Even though she remained very short, her height increased from 35 cm to 73 cm over 2 years and 4 months after starting treatment. Mild loss of fat tissue was seen where the treatment was injected.

- Overall, asfotase alfa treatment benefited all these children, who showed significant improvements in physical symptoms and growth patterns. Some participants experienced mild side effects at injection sites, such as a condition called lipoatrophy (a term describing the localized loss of fat tissue) and redness.

What do the results of this study mean?

- This study the use of asfotase alfa for children and adolescents who show the first signs of HPP before birth or during infancy and childhood.
- Treatment with asfotase alfa can boost growth and effectively manage the symptoms of HPP, including physical performance improvement.

What were the findings of Study 3 in adults with HPP in clinical practice?

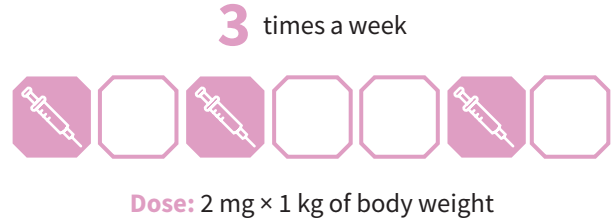
- The study examined how well asfotase alfa works in adults with HPP who began experiencing symptoms in childhood.
- The researchers looked at the impact of continuous treatment with asfotase alfa on people's movement, strength, and walking ability, quality of life, and blood test results over a 2-year period.

How was the study carried out?

- The study took place at a single center in Germany.
- Participants joined the study between August and December 2018.
- Participants attended study appointments at 3 and 6 months from the start of the study, and then every 6 months. Study assessments were based on the standard medical care provided at the center.

How was asfotase alfa administered?

- Treatment
  - People received asfotase alfa as directed on the product label: 2 milligrams for each kilogram of body weight, three times a week.
  - They had been receiving asfotase alfa for at least 12 months before assessment in the study.

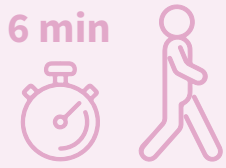


What did the researchers look at?

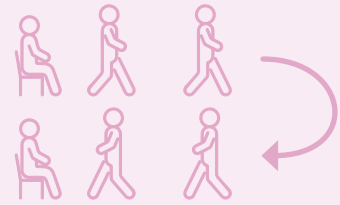
To find out how effective and safe asfotase alfa was, the researchers looked at:

Physical function

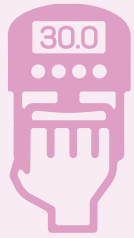
6-minute walk test
Measures the distance a participant can walk in 6 minutes.



Timed up-and-go test
Measures the time taken to stand up from a chair, walk a short distance, turn around, walk back, and sit down.

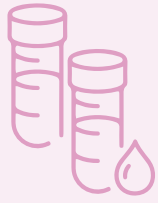


Hand grip strength
Measured using a handheld device.

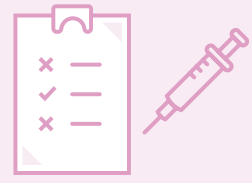


Quality of life
Participants completed questionnaires to assess how HPP affected their quality of life and pain levels.

Laboratory tests
Regular blood tests and other lab assessments were performed to monitor various health parameters important for managing HPP.



Side effects
Any negative reactions or issues experienced during treatment, particularly at the injection site, were recorded.



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Timed up-and-go test:
A test that measures mobility and balance. It involves standing up from a chair, walking a short distance, turning around, walking back, and sitting down. It helps assess physical function in people with conditions affecting movement, like HPP.

Hand grip strength:
A measure of hand and forearm muscle strength, assessed using a handheld device. It helps evaluate overall muscle function and physical performance in people with conditions like HPP.

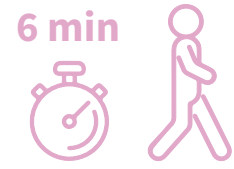
What were the characteristics of the people who took part in the study?

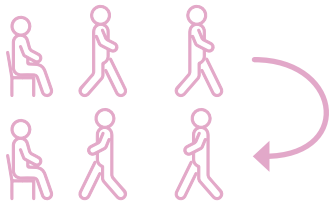
- 22 adults (17 women and 5 men) took part in the study.
  - Their average age at starting asfotase alfa was approximately 49 years old.
- All 22 people had problems with their bones related to HPP: 21 had fractures, and 1 had changes to the shape of bones
- 21 people (95.5%) had movement issues related to HPP, with 20 (91%) experiencing muscle weakness that limited daily activities.
- 21 people (95.5%) had problems with their teeth.
- 21 people (95.5%) had experienced pain related to HPP.

What were the main results?

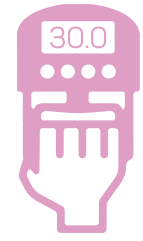
Improvement in physical function

- **Walking distance:**
  - After 1 year from the start of the study:
    - People were able to walk around 30% further in 6 minutes compared to the start of the study.
    - On average, their 6-minute walk distance increased from 266 meters at the start of the study to 347 meters.
  - This improvement was maintained over two years from the start of the study. of the children.



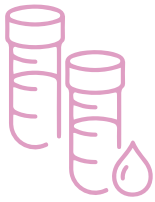


- **Timed up-and-go test:**
  - After 2 years in the study, people were able to complete this test more quickly.
  - The time for this test significantly decreased by 33%, from 18.86 seconds at the start of the study to 12.25 seconds after two years.
  - Improvements occurred as early as 3 months into the study and were sustained for up to 2 years of the study.



- **Handgrip strength:**
  - People's hand strength improved in both hands, including their stronger and weaker hand.
  - Grip strength increased by about 15% in the stronger hand and 20% in the weaker hand.

- **Quality of life:**
  - People's quality of life improved significantly.
  - Improvements occurred as early as 3 months into the study and were sustained for up to 2 years of the study.



- **Laboratory tests:**
  - Blood and urine tests showed changes in substances linked to bone health. This suggests that the bones were repairing and renewing themselves.

What side effects did people experience in the study?

- During the 2 years of asfotase alfa treatment, 22 people reported 114 side effects. Around one-third of these problems (36 out of 114, 32%) were reported as related to the treatment.
- Side effects included discomfort, tingling, and pain, but none were severe.
- The most common side effects were mild reactions at the injection sites reported by 86% of participants, such as:
  - Pain
  - Redness
  - Changes in fat tissue under the skin (lipodystrophy)
- These reactions were frequent but manageable.
- There were no severe side effects. No-one stopped taking the study treatment because of side effects.

Lipodystrophy:
Changes in fat tissue under the skin, which can sometimes occur at injection sites with long-term treatment.

What do the results of this study mean?

- In this study, treatment with asfotase alfa in clinical practice significantly improved physical function, quality of life, and bone health in adults who showed the first signs of HPP in childhood.
- While injection site reactions are common, they are manageable, and the treatment is generally safe and well-tolerated.
- Asfotase alfa therapy can offer substantial benefits and enhance quality of life for people with HPP.

What do the results of the three studies mean?

The combined results of these studies show that asfotase alfa is effective and safe in treating HPP, in people of different ages with different symptoms related to the condition. It improves bone health, physical function, and breathing, and growth in children, making a significant difference in the lives of people living with HPP. These findings support the continued use and further development of asfotase alfa as an important treatment for HPP.

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Where can readers find more information about these studies?

You can read the original articles for free at the links below:

Study 1:

- This article is called: Efficacy and safety of asfotase alfa in infants and young children with HPP.
- The full citation of this article is: Hofmann CE, Harmatz P, Vockley J, *et al.* Efficacy and safety of asfotase alfa in infants and young children with HPP. *The Journal of Clinical Endocrinology & Metabolism* 104(7): 2735–2747 (2019).
- You can read the article for free at: https://academic.oup.com/jcem/article/104/7/2735/5364747

Study 2:

- This article is called: A Japanese single-center experience of the efficacy and safety of asfotase alfa in pediatric-onset hypophosphatasia.
- The full citation of this article is: Sugiyama Y, Watanabe T, Tajika M, *et al.* A Japanese single-center experience of the efficacy and safety of asfotase alfa in pediatric-onset hypophosphatasia. *Orphanet. J. Rare Dis.* 17 (78) (2022).
- You can read the article for free at: https://ojrd.biomedcentral.com/articles/10.1186/s13023-022-02230-y

Study 3:

- This article is called: Effects of asfotase alfa in adults with pediatric-onset hypophosphatasia over 24 months of treatment.
- The full citation of this article is: Seefried L, Genest F, Petryk A, Veith M. Effects of asfotase alfa in adults with pediatric-onset hypophosphatasia over 24 months of treatment. *Bone* 175:116856 (2023).
- You can read the article for free at: https://www.sciencedirect.com/science/article/pii/S8756328223001898

Educational resources

You can find more information about HPP at the following websites:

- **Soft Bones. The US Hypophosphatasia Foundation:** https://softbones.org/wp-content/uploads/2022/01/New-Parent-Guide-to-HPP.pdf
- **National Organization for Rare Disorders (NORD):** https://rarediseases.org/rare-diseases/hypophosphatasia/
- **Orphanet: Hypophosphatasia:** https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=436

Financial disclosure

This plain language summary of publication was funded by Alexion, AstraZeneca Rare Disease.

Competing interests disclosure

Fatma Al Jasmi has received speaker honorarium, and fees for participation in advisory boards from AstraZeneca. Zhanna Belaya declares no conflict of interest related to this article.

Acknowledgments

The authors thank all study participants, investigators, and staff as well as the authors of the three original publications.

Writing disclosure

Dr. Pablo Rivas helped the authors write this PLSP on behalf of Content Ed Net.