Health Technology Briefing
July 2025

Efzimfotase alfa for treating hypophosphatasia

Company/Developer	Alexion Pharmaceuticals Inc.

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 36874	NICE ID: Not Available	UKPS ID: 670753

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Efzimfotase alfa is currently in clinical development for hypophosphatasia (HPP). HPP is a rare, highly variable genetic condition that features abnormalities in the bone and/or tooth mineralisation, caused by a deficiency of an enzyme called tissue-nonspecific alkaline phosphatase (TNSALP). This plays a key role in creating and maintaining healthy bones and managing calcium and phosphate in the body. The reduction of this enzyme's activity leads to ricket-like symptoms, softening and weakening of the bones and a greater incidence of fractures. The signs and symptoms of HPP vary widely and can appear anytime from before birth to adulthood. Currently, there is only one approved treatment for HPP for individuals who develop the condition at an early age before adulthood, which requires frequent dosing. Therefore, there is a need for alternative treatment options for HPP to expand patient choice.

Efzimfotase alfa is a type of artificially created version of a naturally produced enzyme (protein), alkaline phosphatase, which is crucial for various bodily functions, particularly for bone development and maintenance. Efzimfotase alfa works by replacing the alkaline phosphatase that the body needs to free phosphate. This allows it to bind together with calcium to build healthy bones. Efzimfotase alfa is administered via a two-weekly injection under the skin. If licensed, efzimfotase alfa would provide an alternative treatment option for HPP patients.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

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Proposed Indication

Treatment of hypophosphatasia (HPP) in children, adolescents and adult patients.[1-3]

Technology

Description

Efzimfotase alfa (ALXN1850) is a second-generation tissue-nonspecific alkaline phosphatase enzyme replacement therapy.[4] It is a type of recombinant alkaline phosphatase, meaning it is an artificially created version of a naturally produced enzyme, alkaline phosphatase, which is crucial for various bodily functions, particularly for bone development and maintenance.[5] Structurally related to asfotase alfa (given as an injection to treat HPP in children), efzimfotase alfa has undergone several structural modifications. As such, efzimfotase alfa is a soluble glycoprotein that consists of two polypeptide chains of 724 amino acids comprising three segments: the catalytic domain of human tissue-nonspecific alkaline phosphatase; a human IgG2/4 fragment crystallizable domain to facilitate purification and extend half-life; and a deca-aspartate peptide, which enhances affinity to the bone. These structural modifications have the potential to enhance enzymatic activity in substrate hydrolysis and improve the pharmacokinetic profile.[4]

Efzimfotase alfa is currently in clinical development for the treatment of HPP. In the phase III clinical trials (HICKORY, NCT06079281; MULBERRY, NCT06079359; CHESTNUT, NCT06079372), participants are administered efzimfotase alfa subcutaneously every 2 weeks at bodyweight-dependent doses of either 20mg, 35mg or 50mg, for 24 weeks, followed by an open label extension period.[1-3]

Key Innovation

Asfotase alfa is the only approved treatment for HPP for paediatric onset patients (those who develop the condition at an early age before adulthood). Efzimfotase alfa has been developed to address the unmet needs of asfotase alfa, which are to increase drug exposure and make enzyme activity more efficient, thereby enabling study drug dosing at lower volumes and less frequently.[5,6] In vitro, efzimfotase alfa hydrolyses inorganic pyrophosphate approximately twice as fast as asfotase alfa. Hydrolysis activity for pyridoxal 5′-phosphate is also higher for efzimfotase alfa than for asfotase alfa. The structural modifications in efzimfotase alfa and improvements in its posttranslational modifications support lower doses and reduce injection volume and dosing frequency compared with asfotase alfa, all of which may translate to fewer injection site reactions and improved patient treatment experience.[4]

If licensed, efzimfotase alfa would offer a new treatment option for HPP patients, with the potential benefit of reduced dosing frequency compared to current therapies.

Regulatory & Development Status

Efzimfotase alfa does not currently have Marketing Authorisation in the EU/UK for any indication.

Efzimfotase alfa is not in phase II/III clinical development for any other indication.

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Patient Group

Disease Area and Clinical Need

HPP is a rare, inherited metabolic disease caused by deficient activity of tissue-nonspecific alkaline phosphatase, a cell-surface phosphohydrolase expressed mainly in the bone, kidney, and liver.[4] Diminished tissue-nonspecific alkaline phosphatase activity promotes extracellular accumulation of the enzyme's substrates, including inorganic pyrophosphate, a potent inhibitor of bone mineralisation, and pyridoxal 5′-phosphate, the active coenzyme form of vitamin B6.[4] A deficiency of tissue-nonspecific alkaline phosphatase enzyme activity and the accumulation of its substrates can lead to impaired bone mineralisation (osteomalacia or rickets), fractures and pseudo fractures that heal poorly, impaired mobility, abnormal gait, musculoskeletal pain, chondrocalcinosis, muscle weakness, pain, fatigue, premature loss of deciduous teeth and other dental abnormalities, abnormal calcium and phosphate metabolism (for example, hypercalcemia), and renal manifestations (hypercalciuria and nephrocalcinosis).[4] Many clinical manifestations are similar between paediatric and adult patients, although some differences exist, particularly in infants with HPP. Affected infants often present with respiratory complications, craniosynostosis, vitamin B6-responsive seizures, failure to thrive, widespread impaired bone mineralisation, rickets, and bone deformities.[4]

In England, 2023-24, there were 3,270 finished consultant episodes (FCE) and 2,545 admissions for disorders of phosphorus metabolism and phosphatases (ICD-10 code E83.3), which resulted in 4,330 FCE bed days and 836 day cases.[7] The prevalence of life-threatening forms of HPP (that is, those which present at birth or in early childhood), is unknown in England. Other (non-life-threatening) forms, in which signs and symptoms have a later onset, are more common and their genetic prevalence is estimated to be 1 per 6,370 of the population. It is estimated that between 1 and 7 people are diagnosed with perinatal- and infantile-onset HPP each year in England.[8]

Recommended Treatment Options

NICE currently recommends asfotase alfa for the treatment of paediatric-onset HPP.[9]

Clinical Trial Information

Trial	**HICKORY; NCT06079281;** A Phase 3, randomised, double-blinded, placebo-controlled, multicentre study to evaluate efficacy and safety of ALXN1850 (recombinant alkaline phosphatase) administered subcutaneously in adolescent (12 to < 18 years of age) and adult participants with hypophosphatasia who have not previously been treated with asfotase alfa **Phase III** - Active, not recruiting **Location(s):** Five EU countries, UK, USA, Canada and other countries **Primary completion date:** July 2025
Trial Design	Randomised, parallel assignment, placebo-controlled, quadruple-blind
Population	N = 124 (actual); participants with a diagnosis of HPP; aged 12 to 130 years
Intervention(s)	Efzimfotase alfa administrated every 2 weeks (q2w) via subcutaneous (SC) injection at bodyweight dependent doses of either 20mg, 35mg or 50mg, for 24 weeks. Participants will enter the open-label extension (OLE) period and continue q2w dosing with efzimfotase alfa for up to 132 weeks

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Comparator(s)	Matched placebo for 24 weeks. Participants will enter the OLE period and receive bodyweight dependent doses of either 20mg, 35mg, or 50mg of efzimfotase alfa and continue q2w dosing with efzimfotase alfa for up to 132 weeks
Outcome(s)	Primary outcome measure: Change from baseline in 6-minute walk test at the end of the randomised evaluation period (day 169) [Time frame: baseline, day 169] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**MULBERRY; NCT06079359;** A Phase 3, randomised, double-blinded, placebo-controlled, multicentre study to evaluate efficacy and safety of ALXN1850 versus placebo administered subcutaneously in paediatric (2 to < 12 years of age) participants with hypophosphatasia who have not received previous treatment with asfotase alfa **Phase III** - Recruiting **Location(s):** Eight EU countries, UK, USA, Canada and other countries **Primary completion date:** December 2025
Trial Design	Randomised, parallel assignment, placebo-controlled, quadruple-blind
Population	N = 30 (estimated); participants with a diagnosis of HPP; aged 2 to 11 years old
Intervention(s)	Efzimfotase alfa administrated q2w via SC injection at bodyweight dependent doses of either 20mg, 35mg or 50mg, for 24 weeks. Participants will enter the OLE period and continue q2w dosing with efzimfotase alfa for up to 132 weeks
Comparator(s)	Matched placebo q2w for a total of 24 weeks. Participants will enter the OLE period and continue q2w dosing with efzimfotase alfa for up to 132 weeks
Outcome(s)	Primary outcome measure: Radiographic Global Impression of Change (RGI-C) Score at the end of the randomised evaluation period (day 169) [Time frame: day 169] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**CHESTNUT; NCT06079372;** A phase 3, randomised, open-label, parallel-arm, active-controlled, multicentre study to evaluate safety and efficacy of ALXN1850 versus asfotase alfa administered subcutaneously in paediatric participants (2 to < 12 years of age) with hypophosphatasia (HPP) previously treated with asfotase alfa **Phase III** - Active, not recruiting **Location(s):** UK, USA, Canada and other countries **Primary completion date:** August 2025

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Trial Design	Randomised, parallel assignment, placebo-controlled, open-label
Population	N = 42 (actual); participant has diagnosis of HPP; aged 2 to 11 years old
Intervention(s)	Efzimfotase alfa administrated at bodyweight dependent doses of either 20mg, 35mg or 50mg once q2w via SC injection. During Part A of the OLE period, participants will have frequent visits over the first 24 weeks; Part B of the OLE period participants will have visits every 9 months for up to approximately 108 weeks.
Comparator(s)	Participants will receive asfotase alfa for a total of 24 weeks. Participants will receive 6 mg/kg/week of asfotase alfa via SC injection as either 2 mg/kg 3 times per week or 1 mg/kg 6 times per week. In Part A of the OLE period, participants will have frequent visits over the first 24 weeks; in Part B participants will have visits every 9 months for up to approximately 108 weeks.
Outcome(s)	Primary outcome measure: Number of participants with treatment-emergent adverse events (TEAEs) [Time frame: baseline through day 169] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	NCT04980248; A Phase 1, open-label, dose-escalating study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of ALXN1850 in adults with hypophosphatasia **Phase I** - Completed **Location(s):** USA **Study completion date:** August 2022
Trial Design	Sequential assignment, open-label
Population	N = 15 (actual); participants with confirmed clinical diagnosis of HPP; aged 18 to 64 years
Intervention(s)	Efzimfotase alfa in doses of 15 mg, 45 mg, or 90 mg as one intravenous (IV) dose followed by 3 weekly SC doses.[4]
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure: Number of participants with TEAEs and treatment emergent serious adverse events (TESAEs) [Time frame: day 1 up to day 85] See trial record for full list of other outcomes.
Results (efficacy)	Peak and total exposures of efzimfotase alfa increased in a greater-than-dose proportional manner over the range of 15–90 mg after IV and SC dosing. The arithmetic mean elimination half-life was approximately 6 days; absolute bioavailability was 28.6%–36.8% over the SC dose range of 15–90 mg. Dose-

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	dependent reductions in plasma concentrations of inorganic pyrophosphate and pyridoxal 5′-phosphate relative to baseline reached in the first week after IV dosing and were sustained for 3–4 weeks after the last SC dose. Four (27%) participants tested positive for antidrug antibodies (ADAs), 3 of whom were ADA positive before the first dose of efzimfotase alfa. ADAs had no apparent effect on efzimfotase alfa pharmacokinetics/pharmacodynamics. No participants had neutralizing antibodies.[4]
Results (safety)	TEAEs occurred in 12 (80%) participants. Eight (53%) participants had injection site reactions, observed after 10 of 41 (24%) SC injections. Most injection site reactions TEAEs were mild and resolved within 1–2 days.[4]

Estimated Cost

The cost of efzimfotase alfa is not yet known.

Relevant Guidance

NICE Guidance

- NICE highly specialised technologies guidance. Asfotase alfa for treating paediatric-onset hypophosphatasia (HST23). March 2023.

NHS England (Policy/Commissioning) Guidance

No relevant guidance found.

Other Guidance

- Cárdenas-Aguilera, J.G., González-López, V., Zarante-Bahamón, A.M. et al. Diagnosis, treatment, and follow-up of patients with hypophosphatasia. 2025.[10]
- HPP International Working Group. Proposed diagnostic criteria for the diagnosis of hypophosphatasia in children and adolescents. 2023.[11]
- The Japanese Society for Paediatric Endocrinology. Clinical Practice Guidelines for Hypophosphatasia. 2020.[12]
- American Society for Bone and Mineral Research. Hypophosphatasia in Adults: Clinical Assessment and Treatment Considerations. 2017.[13]

Additional Information

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