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REVIEW

Key Learnings from Clinical Research and Real-World Evidence on Asfotase Alfa Effectiveness in Hypophosphatasia: 10 Years Post-Approval

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ABSTRACT

First reported in 1948, hypophosphatasia (HPP) is a rare systemic disease caused by deficient activity of tissue-nonspecific alkaline phosphatase (ALP) enzyme. Patients with HPP experience skeletal and dental manifestations such as rickets/osteomalacia, fractures, pseudofractures, and premature tooth loss, as well as nonskeletal symptoms such as pain and muscle weakness, which result in impaired mobility and poor quality of life. For decades, no specific treatment was available for HPP and the disease was often fatal in infants. Asfotase alfa is a tissue-nonspecific ALP enzyme replacement therapy (ERT) that received first regulatory approval in 2015 in Japan, the European Union, and the United States for the treatment of HPP. This review draws from clinical trial findings, real-world evidence, and relevant case study data demonstrating the safety and effectiveness of asfotase alfa in improving a broad range of skeletal and nonskeletal manifestations in both pediatric and

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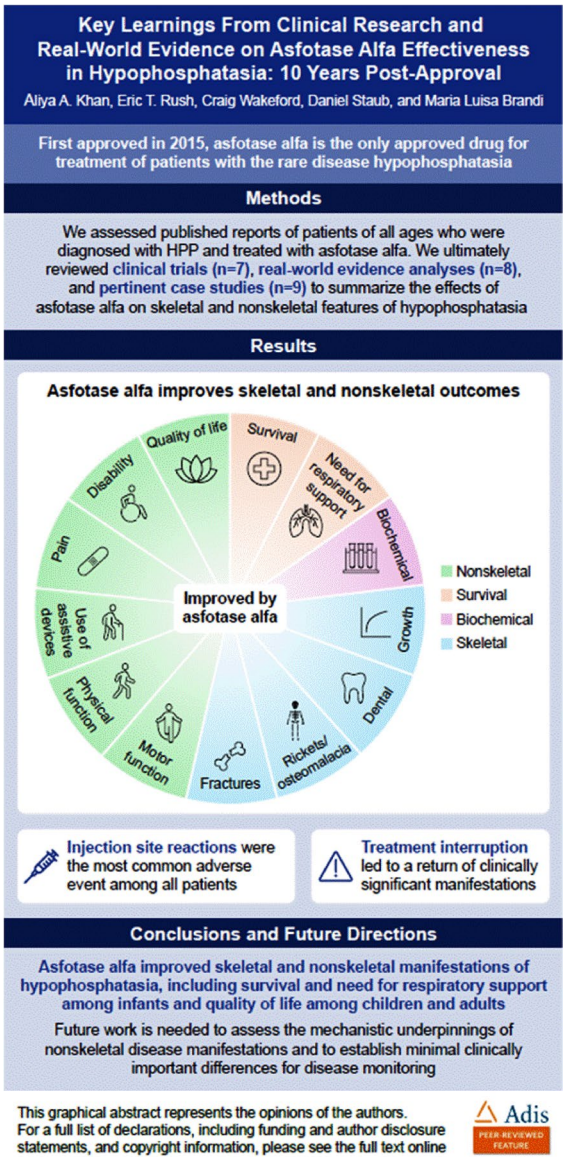
adult patients. Asfotase alfa has been shown to be well tolerated, with manageable side effects. Further, asfotase alfa treatment has improved survival and respiratory outcomes, skeletal outcomes, physical and motor function, pain, disability, and quality of life in patients with HPP. This evidence-based review aims to generate a foundation for improving the understanding of disease pathophysiology, hence enhancing the effectiveness of ERT in patients with HPP.

PLAIN LANGUAGE SUMMARY

We conducted this research to understand the efficacy in clinical trials, effectiveness in real-world studies, and overall safety of asfotase alfa. Asfotase alfa is a treatment for hypophosphatasia, a rare disease identified in 1948. This review marks 10 years since asfotase alfa's first approval in 2015. Hypophosphatasia leads to a variety of health issues, including bone problems like rickets and fractures, premature tooth loss, and muscle weakness, pain, and poor quality of life. Before asfotase alfa, there was no specific treatment, and the disease could be deadly in infants. We gathered and analyzed data from clinical trials, real-world patient experiences, and case studies. This comprehensive review focused on various outcomes in both children and adults with hypophosphatasia. We looked at survival rates, the need for respiratory support, improvements in bone and dental health, physical abilities, pain, disability, and overall quality of life. We also reviewed the safety of asfotase alfa. The findings from the past decade show that asfotase alfa is effective in managing the wide range of symptoms associated with hypophosphatasia, from bone-related issues to muscle weakness. It has significantly improved survival in infants showing symptoms before six months of age. Asfotase alfa has also enhanced patients' quality of life. These results provide a solid base for healthcare providers to assess and treat hypophosphatasia and guide future research directions to further benefit patients.

Graphical Abstract:



Keywords: Asfotase alfa; Bone; Effectiveness; Hypophosphatasia; Quality of life; Treatment

Key Summary Points

Asfotase alfa is the first and only approved drug for the treatment of patients with hypophosphatasia (HPP).

Treatment with asfotase alfa increases overall survival, decreases the requirement for ventilatory support, and improves skeletal outcomes in infants and young children with HPP.

Accumulated real-world data from the past decade of prospective and retrospective studies complement clinical trial data and support the effectiveness of asfotase alfa in improving both skeletal and nonskeletal outcomes, including physical and motor function, pain and disability, and quality of life in children and adults with HPP.

The safety of asfotase alfa has been documented in patients with HPP who were enrolled in clinical trials and in real-world analyses; injection-site reactions are the most common adverse event reported with treatment.

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/https://doi.org/10.6084/m9.figshare.29467706.

INTRODUCTION

HPP is a rare, inherited, systemic metabolic disease that affects people of all ages with a broad range of clinical manifestations, high disease burden, and substantial negative impact on quality of life (QoL) [1–3]. The first case of hypophosphatasia (HPP) was reported in 1948 by John Rathbun [4]. The patient, a 3-week-old infant, presented with weight loss, severe rickets, undermineralized bone, and seizures that clinically resembled those seen with other skeletal disorders such as osteogenesis imperfecta. However, the patient also presented with low alkaline phosphatase (ALP) activity, which suggested a novel disease [4]. For decades, there was no specific treatment for HPP and the disease was often fatal in infants [5, 6]. The tissue-nonspecific ALP enzyme replacement therapy (ERT) asfotase alfa (Strensiq®; Alexion, AstraZeneca Rare Disease, Boston, MA, USA) was the first drug developed for treatment of HPP and is currently the only treatment available specifically for this disease. Asfotase alfa received regulatory approval in 2015 in Japan for the treatment of patients with HPP and in the United States and the European Union for the treatment of patients with pediatric-onset HPP [7–10]. In the European Union, asfotase alfa is indicated for patients with pediatric-onset HPP to treat the bone manifestations of the disease [8].

Signs and symptoms of HPP are variable, although age at clinical presentation or diagnosis is moderately associated with different sets of symptoms [1, 2, 11]. In infants, clinical manifestations of HPP may include respiratory failure and vitamin B_6-responsive seizures historically leading to high morbidity and mortality [11, 12]. Children can present with rickets, failure to thrive, craniosynostosis, early nontraumatic loss of primary teeth with intact roots, and delayed motor milestones [11, 13, 14]. Adults with HPP may also have a history of these conditions or may not have significant manifestations until adulthood [11, 15]. Manifestations that are more common among adults include fractures and pseudofractures (particularly metatarsal and atypical femoral), impaired fracture/pseudofracture healing, chondrocalcinosis and other rheumatic manifestations, including pain and muscle weakness [1, 16, 17]. Manifestations that are common in both children and adults include impaired mobility, muscle weakness, fatigue, chronic musculoskeletal pain, nephrocalcinosis, and dental problems [2, 11].

HPP is typically caused by variants in *ALPL,* the gene encoding tissue-nonspecific ALP. The diagnosis of HPP is made based on low serum

ALP activity, which is indicative of tissue-nonspecific ALP activity in tissues, and clinical and radiographic disease manifestations [18, 19]. Genetic testing is often used, when available, although it is not required to confirm HPP diagnosis. More than 400 *ALPL* variants with variable penetrance and expressivity have been identified in patients with HPP, contributing to the heterogeneous clinical manifestations of the disease [20, 21]. Variants in *ALPL* may be inherited in an autosomal dominant (monoallelic) or autosomal recessive (biallelic) manner, with autosomal recessive inheritance more frequently found in patients who present with life-threatening symptoms before 6 months of age [16, 20, 22]. Patients with autosomal dominant inheritance may carry variants that exert a dominant-negative effect, thereby reducing ALP activity [23, 24]. The comprehensive HPP genetic analysis in the Global *ALPL* Gene Variant Classification Project [24] has provided some insight into the broad spectrum of phenotypic variability associated with *ALPL* variants, although the correlation between genotype and phenotype in HPP requires further investigation.

While infants who present with symptoms in the first 6 months of life may have life-threatening disease, the burden of disease is often similar between patients who first manifest HPP in childhood, after 6 months of age, and adult patients [3, 14, 25]. Disease burden is uniformly high for patients regardless of number of *ALPL* variants, presence or absence of skeletal manifestations, and, to some extent, age at first disease presentation [3, 20, 25, 26]. Patients with biallelic disease report skeletal, dental, muscular, and neurologic manifestations more frequently than patients with monoallelic disease, although patient-reported outcomes seem to be similar among both groups [26]. In addition, patients who first experience symptoms of HPP in childhood report comparable numbers of fractures sustained over their lifetime and use of adaptive strategies to overcome disability compared with those who first experience symptoms of HPP in adulthood [3].

The clinical manifestations of HPP are attributed to the downstream effects of deficient ALP. Inorganic pyrophosphate (PPi) is dephosphorylated by ALP in a reaction that releases inorganic phosphate (Pi) [19]. Thus, deficient ALP activity leads to extracellular accumulation of PPi, a key inhibitor of bone mineralization, and reduced production of Pi [2, 19, 27]. Hydroxyapatite formation is impacted by extracellular PPi accumulation and the altered ratio of PPi to Pi, leading to poor mineralization of bones and teeth and related sequelae, including increased risk of fractures or pseudofractures, bone deformities, and premature loss of teeth [2, 15, 19, 27–29]. PPi is also involved in crystal formation in the synovial fluid, contributing to conditions such as calcium pyrophosphate deposition disease [30]. In addition to PPi, pyridoxal 5′-phosphate (PLP), the circulating form of vitamin B_6, is dephosphorylated by ALP to form pyridoxal (PL) [19]. This dephosphorylation of PLP is necessary for cellular uptake of vitamin B_6. Once inside the cell, PL is rephosphorylated to PLP to resume its active role within cellular processes [31]. Intracellular PLP deficiency secondary to deficient ALP activity is associated with vitamin B_6-responsive seizures in infants with HPP, and evidence from preclinical models of HPP suggests a role for PLP in muscular function [19, 32]. Phosphoethanolamine (PEA) is an additional known substrate of ALP. While the clinical consequences of PEA accumulation in HPP are not completely understood, detection of elevated urinary PEA can help support a diagnosis in individuals with suspected HPP, making it a useful assessment tool [33]. Patients with HPP who have biallelic disease typically have greater elevations of PPi and PLP than monoallelic patients, although disease burden can be significant regardless of *ALPL* variant state [20, 26].

Asfotase alfa functionally replaces deficient ALP enzyme activity, thus treating the direct cause of HPP manifestations [7]. Clinical research and real-world evidence analyses have generated data on short- and long-term safety and efficacy of asfotase alfa. This review summarizes the accumulated data on safety, clinical efficacy, and real-world effectiveness of

asfotase alfa 10 years post-approval. The information highlighted in this review is intended to enhance awareness among healthcare professionals and provide the most current data in the hope of optimizing care of pediatric and adult patients with HPP. This review article did not require institutional review board or institutional animal care and use committee approval, as it is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

OUTCOMES OF ASFOTASE ALFA TREATMENT

The earliest data showing the efficacy of asfotase alfa were from animal models of HPP. A murine model with homozygous knockout of tissue-nonspecific ALP (*Alpl*$^{-/-}$) was developed in 1997 that recapitulated the HPP phenotype seen in human infants, including weight loss and seizures [34]. Asfotase alfa treatment restored normal skeletal morphology and prevented lethal seizures in *Alpl*$^{-/-}$ mice [35]. In subsequent analyses, asfotase alfa treatment rescued craniofacial bone and root dentin mineralization, as well as defective enamel formation in teeth of *Alpl*$^{-/-}$ mice [36–38]. Recent preclinical studies have shown subtle advantages of initiating prenatal asfotase alfa treatment rather than starting treatment at birth [39, 40].

Disease assessments in patients with HPP typically include clinical and radiographic evaluations to assess for rickets, pseudofractures, or fractures (Tables 1, 2) [5, 6, 20, 29, 41–76], and laboratory data to assess alterations in serum levels of HPP biomarkers [19]. These clinical, radiographic, and biochemical endpoints are often used to evaluate ERT effectiveness in clinical trials and observational studies. Assessment of patients with HPP has historically focused on the radiologically demonstrated effects on bone pathology and, among infants with life-threatening disease, overall survival. The emergence of new assessment methods, better understanding of disease burden across all ages, and availability of ERT have prompted rethinking of how patients with HPP are diagnosed and evaluated. While increasing survival among infants remains an important treatment goal in this age group, the clinical focus has expanded to address improving nonskeletal outcomes, including physical and motor function, mobility, pain, and disability in patients with late-onset (first manifestations after 6 months of age), non–life-threatening HPP, because of their significant impact on patients' QoL.

Survival and Respiratory Support

Survival was low among untreated patients who manifested signs and symptoms of HPP before 6 months of age (early-onset HPP) but was greatly improved by asfotase alfa treatment [5, 12, 76]. In a retrospective chart review of untreated patients with HPP, 73% (35/48) who developed life-threatening symptoms of HPP before 6 months of age died before reaching 14 months of age [12]. In another analysis of data from patients with life-threatening disease, survival after 1 year was 95% among patients treated with asfotase alfa compared with only 42% among historical controls (Fig. 1A) [5]. In a 5-year real-world analysis of asfotase alfa effectiveness, which included 6 patients younger than 1 year of age, all patients survived after initiating asfotase alfa treatment, highlighting the impact of treatment on survival [76].

Patients with life-threatening, early-onset HPP frequently require respiratory support owing to hypomineralization of the ribs and pulmonary hypoplasia, both of which can cause respiratory failure [6, 65, 77]. Types of respiratory support include use of supplemental oxygen, continuous positive airway pressure, biphasic positive airway pressure, or tracheostomy with mechanical ventilation [5, 6, 65, 69]. Across four studies, the percentage of patients who required respiratory support before starting asfotase alfa treatment ranged from 35% to 91% (Fig. 1B) [5, 6, 65, 69]. In these studies, asfotase alfa treatment decreased dependence on respiratory support, with one study showing that only 10% of patients still needed support at last follow-up

Table 1 Clinical endpoints assessed in patients with HPP

Method	Description
Bone	
RGI-C (Radiographic Global Impression of Change)	Validated 7-point scoring system to measure skeletal manifestations in infants and children; evaluates changes in irregularity of the provisional zone of calcification, physeal widening, metaphyseal flaring, fraying, radiolucencies, altered osteosclerosis, altered ratio of mid-diaphyseal cortex-to-bone thickness, gracile bones, absence of some or all bones, and recent fractures [42]
Age range	Children ≤ 12 years
Change indicating improvement	Increased score
RSS (Rickets Severity Scale)	Rates growth plate abnormalities at the wrists and knees on a 11-point scale [43]
Age range	Children aged 1–14 years
Change indicating improvement	Decreased score
Physical function	
6MWT (6-Minute Walk Test)	Validated measure of how far an individual is able to walk on a hard, flat surface during 6 min; measures walking endurance and fatiguability [44, 45]. An MCID of 31 m for children aged 5–12 years, 33 m for adolescents aged 13–17 years, and 31 m for adults aged ≥ 18 years has been established [45]. Results are reported as an absolute value in meters or as percent predicted for age, with a value < 80% indicating subnormal [64]
Age range	Children and adults aged ≥ 5 years
Change indicating improvement	Increased (larger) distances; increased percent predicted
Bleck Scale	Rates patients on a 9-point scale ranging from a score of 1 for being unable to walk to 9 for being able to walk the same distance as their age-adjusted peers without crutches or canes [46–48]
Age range	Children and adults aged ≥ 2 years of age
Change indicating improvement	Increased scores
TUG (Timed Up-and-Go)	Measures the time taken for an individual to stand up from a standard armchair, walk a distance of 3 m, turn, walk back to the chair, and sit down again while wearing usual footwear and any customary walking aid [49]
Age range	Adults ≥ 18 years; test is validated in frail individuals aged 70–84 years

Table 1 continued

Method	Description
Change indicating improvement	Faster (shorter) times
SPPB (Short Physical Performance Battery)	Performance measure consisting of a balance test, gait speed, and a repeated Chair-Rise Test, summarized on a 12-point scale [52] The repeated Chair-Rise Test measures the time taken for the patient to stand and sit down again 5 times as quickly and safely as possible, with hands folded across the chest [50–52]. The test assesses functional mobility, with a focus on the axial skeleton and hip joint [51]
Age range	Adults aged ≥ 18 years; test is validated in adults aged ≥ 65 years
Change indicating improvement	Increased summary score; faster (shorter) times for gait speed and repeated chair-rise test
LEFS (Lower Extremity Functional Scale)	Measures physical function of the lower extremities on an 80-point scale with an MCID of 9 points [41]
Age range	Adolescents and adults aged ≥ 13 years [20, 41]
Change indicating improvement	Increased scores
Motor function	
BSID-III (Bayley Scales of Infant and Toddler Development III)	Validated instrument comprised of 5 subtests for evaluation of developmental functioning; measures both gross and fine motor skills in infants and toddlers [53]
Age range	Children aged 16 days to 42 months
Change indicating improvement	Increased scores
BOT-2 (Bruininks–Oseretsky Test of Motor Proficiency, Second Edition)	Measure of fine and gross motor skills in children and adults aged 4–21 years. The test highlights motor performance in the areas of stability, mobility, strength, coordination, and object manipulation [54]
Age range	Children, adolescents, and adults aged 4–21 years
Change indicating improvement	Increased scores
PDMS-2 (Peabody Developmental Motor Scales, second edition)	Measure of gross and fine motor skills in children. The test includes reflexes, stationary equilibrium, locomotion, object manipulation, grasping, and visual-motor integration [55]
Age range	Children from birth through 5 years of age
Change indicating improvement	Increased scores

Table 1 continued

Method	Description
BAMF (Brief Assessment of Motor Function)	Validated measure of gross and fine motor function of the upper and lower extremities, oral motor deglutition, and oral motor articulation in children [56]
Age range	Infants, adolescents, and adults aged 2 months to 28 years
Change indicating improvement	Increased scores
Disability	
HAQ-DI (Health Assessment Questionnaire-Disability Index)	Measure of functional ability with a focus on activities of daily living, including dressing, rising, eating, walking, maintaining hygiene, reaching, gripping, and completing usual activities. Assessments are made on a scale from 0 (no disability) to 3 (complete disability) [57]
Age range	Adults aged ≥ 18 years
Change indicating improvement	Decreased scores
PODCI (Pediatric Outcomes Data Collection Instrument)	Measure of functional status in children with a focus on musculoskeletal health [58]
Age range	Children aged 2–18 years
Change indicating improvement	Increased scores
Pain	
BPI-SF (Brief Pain Inventory-Short Form)	Self-reported assessment of pain severity in 4 categories (pain at its worst, its least, its average, and pain right now), each reported on a scale from 0 (no pain) to 10 (pain as bad as you can imagine). The BPI also measures pain interference within 7 daily activities (general activity, walking, work, mood, enjoyment of life, relations with others, sleep) [59]
Age range	Adults aged ≥ 18 years
Change indicating improvement	Decreased scores
QoL	
PedsQL (Pediatric Quality of Life Inventory)	Survey determining quality of life in children aged 2 to 18 years that can be completed by the child and/or parent; assessments include 23 items related to physical, emotional, social, and school functioning [60]
Age range	Children aged 2–18 years
Change indicating improvement	Increased scores
SF-36v2 (Short Form-36 version 2)	Survey determining quality of life; assessments include both physical health and mental health [61, 62]

Table 1 continued

Method	Description
Age range	Adolescents and adults aged ≥ 14 years
Change indicating improvement	Increased scores
EQ-5D-3L	Survey determining quality of life; survey comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), which are each rated by the user as no problems, some problems, or extreme problems with scores of 1, 2, or 3. These scores are often then translated to quality-adjusted life-years on a scale from 0 (0 is the health equivalent to death) to 1 (perfect health) [63]
Age range	Adults aged ≥ 18 years
Change indicating improvement	Increased scores

MCID minimal clinically important difference

(up to 5.5 years) [5]. In two of these studies, ventilator-free survival, defined as the percentage of patients who were alive and not receiving ventilator support after asfotase alfa treatment, was achieved in 84% (38/45) and 100% (5/5) of patients [65, 69].

Seizures

Vitamin B_6-responsive seizures are reported in approximately 10% of all children enrolled in the Global HPP Registry, although this proportion is higher among children < 6 months of age [1, 14]. In a small analysis of historical controls who experienced seizures and did not receive ERT, none of the 10 patients survived [5]. However, survival was 77% (10/13) among patients who received asfotase alfa treatment [5]. In a case study, asfotase alfa treatment led to cessation of seizures in an infant who started treatment at post-natal day 2 [78]. The patient experienced seizures again after treatment interruption, which progressed to acute encephalopathy [78]. Seizures were again mitigated upon reinitiation of asfotase alfa treatment [78], suggesting the efficacy of asfotase alfa in preventing seizures in infants with HPP.

Skeletal and Dental Parameters

Fractures

Over one-third of adults assessed in the Global HPP Registry have a history of recurrent and poorly healing fractures [1]. Limited evidence suggests that asfotase alfa treatment can improve fracture healing and reduce fracture incidence in patients with HPP. In a case series of 2 adults with HPP, treatment with asfotase alfa was associated with marked healing of pre-existing fractures. One of these patients had a history of a femoral pseudofracture with little evidence of healing over the course of 17 years, but experienced notable healing 11 months after initiating treatment with asfotase alfa, as evidenced by near resolution [79]. An additional case series of 2 adults with femoral fractures showed that 4–6 months of treatment with asfotase alfa promoted fracture healing [16]. Accelerated fracture consolidation with asfotase alfa was associated with improved clinical symptoms and pain-free normal motor function [79, 80]. In an observational study, 13% (3/24) of adults experienced fractures after 1 year of treatment with asfotase alfa [48]. In contrast, the prevalence of fractures

Table 2 Summary of studies reporting clinical outcomes in HPP with asfotase alfa

Study	Population	Number of enrolled patients	Endpoints		
			Biochemical	Skeletal	Nonskeletal
Whyte et al. 2012 (NCT00744042) [6]	Age ≤ 3 years with symptoms of HPP prior to age 6 months	11		RGI-C and RSS	Respiratory function BSID-III
Whyte et al. 2016 (NCT00744042, NCT01205152, NCT01176266, and NCT01419028) [5]	Age ≤ 5 years with symptoms of HPP prior to age 6 months	48		RGI-C	Overall survival Respiratory function
Whyte et al. 2016 and 2018 (NCT00952484 and NCT01203826) [42, 64]	Age 6–12 years with HPP	13	PPi and PLP	RGI-C and RSS Height, weight, and BMI Z-scores	6MWT BOT-2 PODCI CHAQ
Kitaoka et al. 2017 (NCT02456038) [65]	Patients of any age with an HPP diagnosis	13		Radiology of wrists and knees Height, weight, arm span, head circumference, chest circumference Z-scores	Overall survival Ventilator-free survival Respiratory function in patients with respiratory support Gross motor milestones
Akiyama et al. 2018 [66]	Patients with HPP	20	Plasma PLP, PL, PA, and PLP/PL ratio		

Table 2 continued

Study	Population	Number of enrolled patients	Endpoints		
			Biochemical	Skeletal	Nonskeletal
Whyte et al. 2019 (NCT00744042 and NCT01205152) [67]	Age ≤ 3 years with life-threatening HPP	11	Plasma PPi and PLP and serum intact PTH	RGI-C and RSS	Respiratory support (use of supplemental oxygen, CPAP, BIPAP, mechanical ventilation)
				Length/height, weight, and head circumference Z-scores	BSID-III, PDMS-2, BOT-2
Kishnani et al. 2019 (NCT01163149) [68]	Age 13–65 years with pre-established HPP diagnosis	19	Plasma PLP and PPi	Transiliac crest biopsy	6MWT BOT-2, LEFS BPI-SF
Hofmann et al. 2019 (NCT01176266) [69]	Age ≤ 5 years with signs or symptoms of HPP before age 6 months	69		RGI-C and RSS Length/height, weight, and head circumference Z-scores	Respiratory status Ventilator-free and overall survival
Seefried et al. 2021 (NCT02797821) [70]	Adults ≥ 18 years with pediatric-onset HPP	27	PLP, PPi		
Genest et al. 2020 (NCT03418389) [71]	Adults ≥ 18 years with pediatric-onset HPP	14			6MWT, TUG, SPPB, LEFS SF-36v2 Pain (Likert scale)
Kishnani et al. 2021 (NCT01163149) [20]	Adults and adolescents with HPP	44	PLP, PPi		6MWT LEFS BPI-SF

Table 2 continued

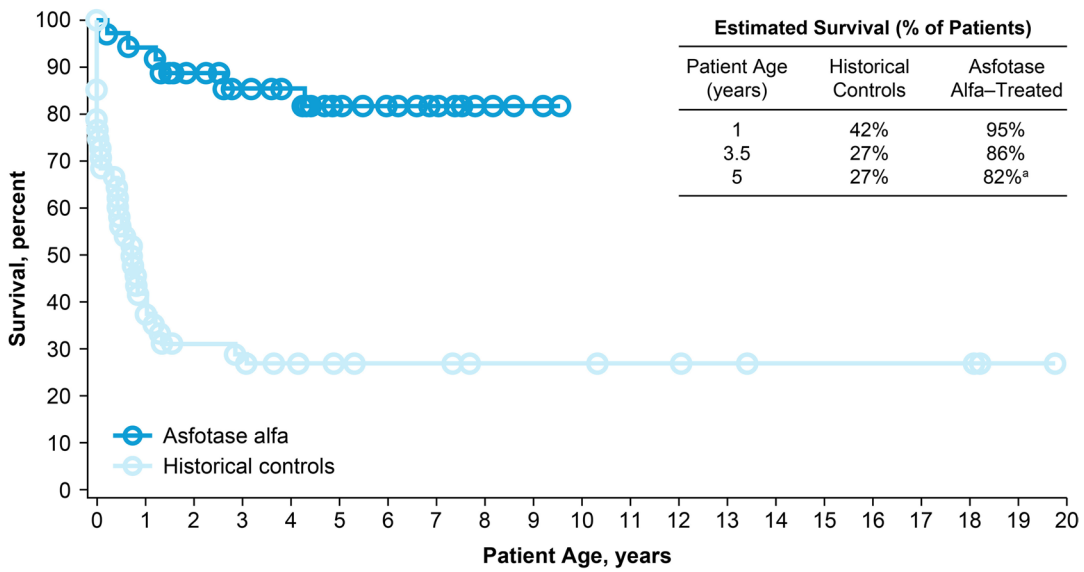
Study	Population	Number of enrolled patients	Endpoints		
			Biochemical	Skeletal	Nonskeletal
Schroth et al. (NCT01176266) [72]	Children with signs or symptoms of HPP before age 6 months	11		Dental exam	
Seefried et al. 2021 (NCT03418389) [29]	Adults ≥ 18 years of age with pediatric-onset HPP	21	PLP; urine PEA/Cr ratio; PTH; calcium; phosphate, FGF-23; osteocalcin; P1NP; TRAP5b; NTx; GFR		
Seefried et al. 2023 (NCT03418389) [73]	Adults ≥ 18 years of age with pediatric-onset HPP	22	ALP, PLP, urine PEA/Cr, PTH, calcium, phosphate, FGF-23, osteocalcin, P1NP, TRAP5b, NTx		6MWT, TUG, SPPB, LEFS, SF-36 Pain (Likert scale)
Kishnani et al. 2023 (NCT02306720) [74]	Patients of all ages with HPP diagnosis	190			6MWT SF-36 HAQ-DI BPI-SF
Dahir et al. 2024 [75]	Adults ≥ 18 years of age with pediatric-onset HPP	50			PHQ-9, WPAI:SHP, PROMIS-29, RAPID3 TSQM

Table 2 continued

Study	Population	Number of enrolled patients	Endpoints		
			Biochemical	Skeletal	Nonskeletal
Padidela et al. 2025 [76]	Age < 18 years with pediatric-onset HPP	24		Length/height and weight percentiles and Z-scores	Respiratory support (supplemental nasal oxygen, CPAP, BiPAP, invasive ventilation) 6MWT, Bleck scale BAMF Analgesic use PedsQL
Moss et al. 2025 [48]	Age ≥ 18 years with pediatric-onset HPP	28		Occurrence of fractures	6MWT, Bleck scale BPI-SF, analgesic use EQ-5D-3L

6MWT 6-Minute Walk Test, *ALP* alkaline phosphatase, *BAMF* Brief Assessment of Motor Function, *BiPAP* biphasic positive airway pressure, *BMI* body mass index, *BOT-2* Bruininks-Oseretsky Test of Motor Proficiency, Second Edition; *BPI-SF* Brief Pain Inventory-Short Form, *CHAQ* Child Health Assessment Questionnaire, *CPAP* continuous positive airway pressure, *FGF-23* fibroblast growth factor-23, *GFR* glomerular filtration rate, *HAQ-DI* Health Assessment Questionnaire–Disability Index, *HPP* hypophosphatasia, *LEFS* Lower Extremity Functional Scale, *mPOMA-G* Modified Performance-Oriented Mobility Assessment-Gait, *NTx* N-terminal telopeptide of type 1 collagen, *P1NP* procollagen type 1 N-propeptide, *PA* pyridoxic acid, *PDMS-2* Peabody Developmental Motor Scales, *PEA/Cr* phosphoethanolamine/creatine, *PedsQL* Pediatric Quality of Life Inventory, *PHQ-9* Patient Health Questionnaire-9, *PL* pyridoxal, *PLP* pyridoxal 5′-phosphate, *PODCI* Pediatric Outcomes Data Collection Instrument, *POMA-G* Performance-Oriented Mobility Assessment-Gait, *PPi* inorganic pyrophosphate, *PROMIS-29* Patient-Reported Outcomes Measurement Information System 29, *PTH* parathyroid hormone, *QoL* quality of life, *RAPID3* Routine Assessment of Patient Index Data 3, *RGI-C* Radiographic Global Impression of Change, *RSS* Rickets Severity Scale, *SF-36* Short-Form Health Survey version 2, *SPPB* Short Physical Performance Battery, *TRAP5b* tartrate-resistant acid phosphatase 5b, *TSQM* Treatment Satisfaction with Medications Questionnaire, *TUG* Timed Up-and-Go, *WPAI:SHP*, Work Productivity and Activity Impairment Questionnaire: Specific Health Problem

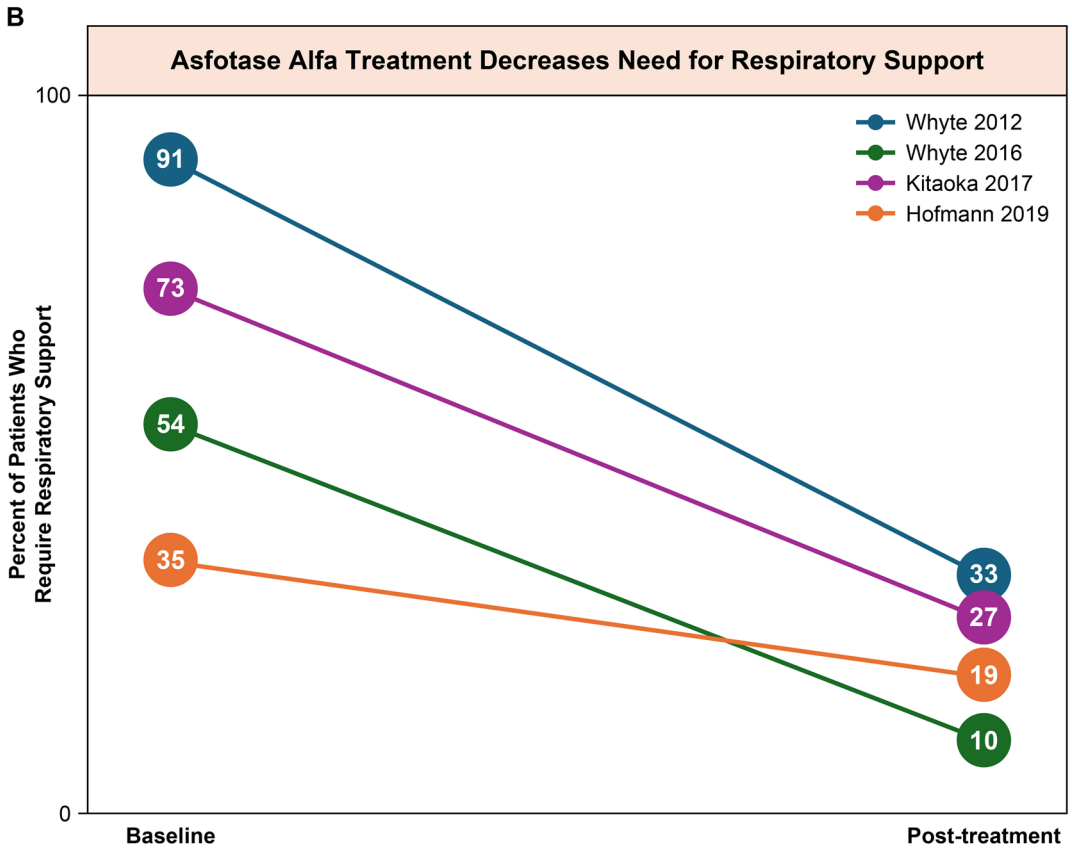
A



Estimated Survival (% of Patients)

Patient Age (years)	Historical Controls	Asfotase Alfa–Treated
1	42%	95%
3.5	27%	86%
5	27%	82%[a]

B



◂**Fig. 1** Asfotase alfa treatment improves survival and decreases need for respiratory support in infants and young children with life-threatening HPP. (**A**) Survival in historical controls and treated patients with life-threatening HPP, reproduced from Whyte et al. 2016, with permission [5]. (**B**) Respiratory support requirement; studies included children with HPP who first displayed signs and symptoms of HPP at age < 6 months [5, 6, 65, 69]. Follow-up time varies as indicated: Whyte et al. 2012—48 weeks; Whyte et al. 2016—up to 5.5 years; Kitaoka et al. 2017—up to 1.8 years; Hofmann et al. 2019—up to 6 years. [a]84% observed survival; 31 of 37 treated patients survived to 5 years of age

among untreated adults has been shown to range from 37% to 95% [1, 73, 81, 82].

Osteomalacia

In another study, osteomalacia was assessed by bone histomorphometry of samples obtained via transiliac bone biopsy in patients 13–66 years of age who received asfotase alfa compared with controls [68]. Mean osteoid volume per bone volume decreased by 0.8% after 1 year of treatment with asfotase alfa but increased by 0.2% after 6 months in untreated patients. Mean osteoid thickness was 109% of that reported in a healthy population at baseline and did not significantly change with asfotase alfa treatment. Baseline mean mineralization lag time in patients with HPP was 891% of that of a healthy population and was significantly decreased by 580% after 1 year of asfotase alfa treatment, suggesting improvement. The improvements in osteomalacia were accompanied by normalization of biomarkers of disease, including median reductions of 2.2 µM in serum PPi and 254.5 ng/mL in serum PLP after 6 months of asfotase alfa treatment. Median PPi concentration among all patients was 3.4 µM (normal range in adults: 1.0–5.8 µM; normal range in adolescents aged 13–18 years: < 0.8–4.8 µM) and median PLP concentration was 39.9 ng/mL (normal range in adults: 2.8–26.7 ng/mL; normal range in adolescents: 5.7–61.2 ng/mL) after 6 months of treatment.

Bone Metabolism Biomarkers

Asfotase alfa treatment significantly improves biochemical markers of bone and mineral metabolism, indicating that treatment-mediated mineralization may enable bone remodeling and turnover of previously unmineralized bone. In one study measuring markers of bone turnover, including osteocalcin, procollagen type 1 N-propeptide, and tartrate-resistant acid phosphatase 5b, transient changes occurred after 3 and 6 months of treatment and reverted to near-baseline levels after 12 months [29]. Statistically significant but transient increases in parathyroid hormone were also observed at 3 and 6 months after initiating asfotase alfa [29]. Serum calcium or phosphorus are sometimes elevated in patients with HPP, although no significant change in either marker was observed over the course of up to 2 years of asfotase alfa treatment [29, 73]. In an independent analysis of adults who first had signs and symptoms of HPP in childhood, asfotase alfa treatment decreased plasma PPi in a dose-dependent manner [70]. Relative to PPi values among patients treated with 0.5 mg/kg asfotase alfa, the least squares mean changes in PPi were – 1.2 µM among patients treated with 2.0 mg/kg asfotase alfa and – 1.9 µM among those treated with 3.0 mg/kg asfotase alfa; similarly, least squares mean changes in PLP were – 29.5 ng/mL and – 34.0 ng/mL, respectively. In this study, normal ranges for PPi and PLP in adults aged > 18 years were 1.0–5.8 µM and 2.8–26.7 ng/mL, respectively [29].

Rickets

Nearly one-third of children with HPP present with rickets before initiating asfotase alfa treatment [14]. The Radiographic Global Impression of Change (RGI-C) is a validated 7-point scale developed for assessment of radiographic features, including rickets, in children with HPP [42]. A 2-point improvement in RGI-C score was observed as early as 6 weeks after asfotase alfa treatment initiation among children in clinical trials; results were sustained at long-term follow-up of 5–7 years (Fig. 2A) [6, 64, 67,

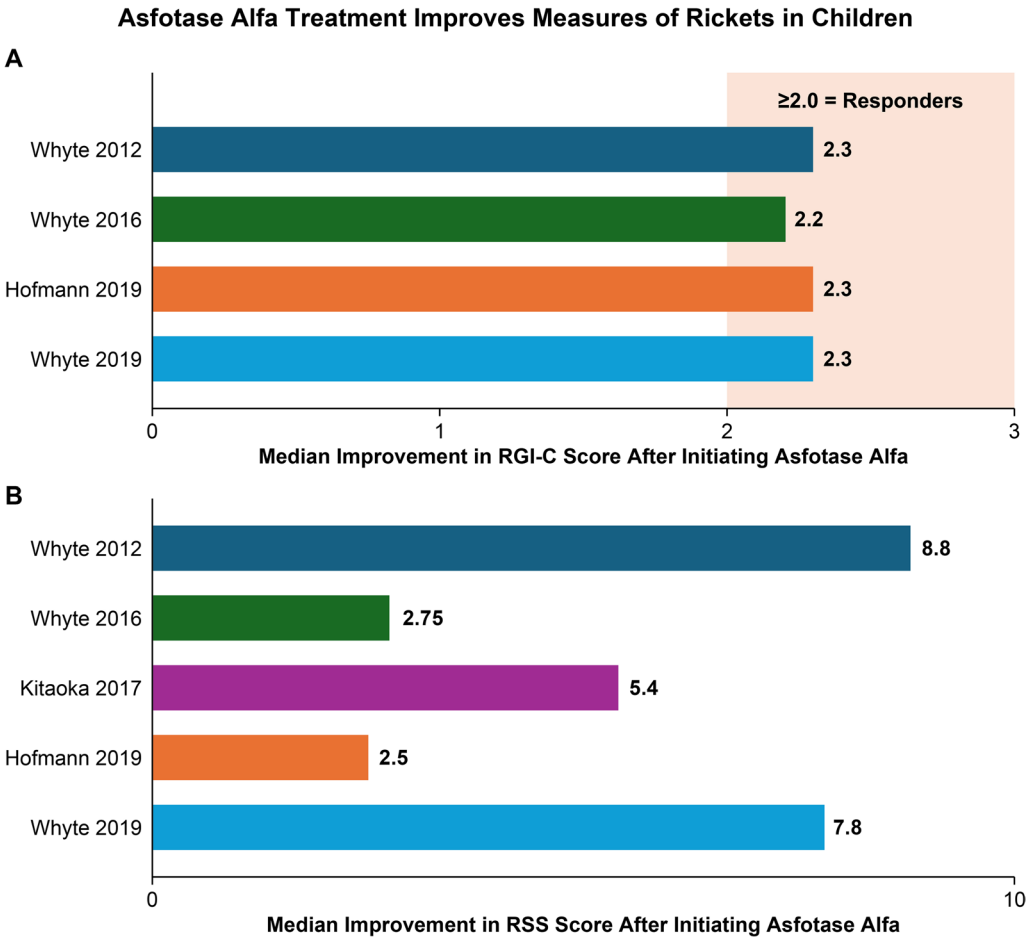


Fig. 2 Asfotase alfa treatment improves measures of rickets in children. Median improvements in (**A**) RGI-C score and (**B**) RSS score. For RGI-C, patients were classified as treatment responders if their score improved by ≥ 2 points, indicating substantial healing [6, 64, 65, 67, 69]. Follow-up times varied as indicated: Whyte et al. 2012—48 weeks; Whyte et al. 2016—5 years; Kitaoka et al. 2017—24 weeks; Hofmann et al. 2019—up to 6 years; Whyte et al. 2019—7 years. *RGI-C* Radiographic Global Impression of Change, *RSS* Rickets Severity Scale

69]. Historical controls showed no improvement in RGI-C score at any time point [64]. In one study, patients achieved an improvement in RGI-C score of 2 points or higher during or shortly after discontinuing ventilatory support, suggesting a link between bone development and respiratory function [5]. Children also experienced significant improvements of up to 3.4 points on the 11-point Rickets Severity Scale (RSS) score after 12 weeks of asfotase alfa treatment, with continued improvements reported at later time points (Fig. 2B) [6, 43, 64, 65, 67, 69]. Skeletal improvements were accompanied by a 79% decrease in serum PPi concentrations to 1.1 nM after 24 weeks of asfotase alfa treatment in children ≤ 3 years of age [6]. Decreased PPi theoretically underlies the improvements in rickets in these patients [19]. The decreases in PPi were maintained through up to 7 years of follow-up [67], but treatment did not affect serum calcium or inorganic phosphate levels [6]. Serum PPi and PLP levels were similarly within normal reference ranges after 6 weeks of treatment in children up to 12 years of age [64, 69].

Growth

Although most children with HPP maintain height and weight Z-scores in the normal range, 17% to 20% of children have short stature (defined as below the third percentile) [13]. Clinical trials and real-world analyses confirm that treatment with asfotase alfa improves length/height and weight Z-scores for children with HPP, although there is heterogeneity in individual patient responses [64, 67, 69, 76]. Improvements in Z-scores from baseline to last assessment ranged from 0.2 to 0.6 standard deviations for height/length and from – 0.07 to 2.4 standard deviations for weight. Improvements in height and weight Z-scores were reported as early as 6 weeks after treatment initiation [64]. Children also had improved body mass index (+ 0.62) and head circumference (+ 0.2) Z-scores with asfotase alfa treatment [64, 69].

Dentition

Premature loss of deciduous teeth with intact roots is a hallmark symptom of HPP reported in approximately half of children and adults with

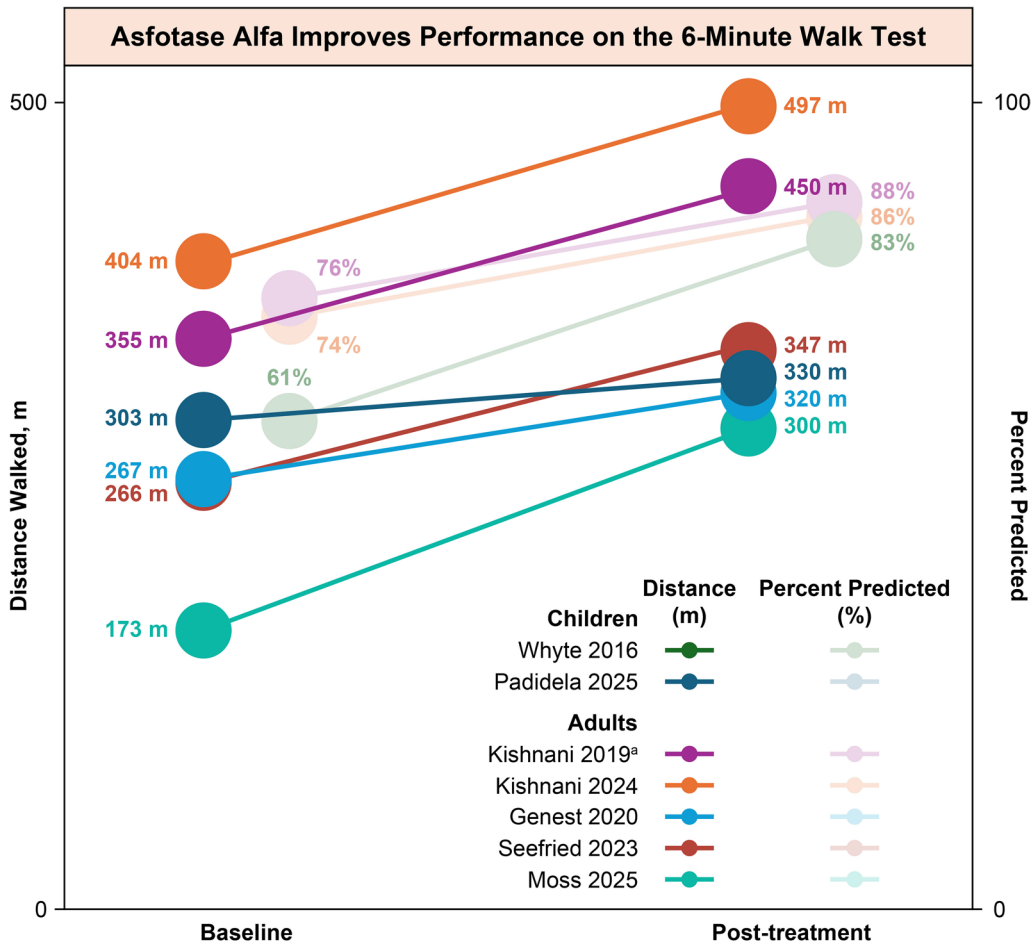


Fig. 3 Asfotase alfa improves performance on the 6-Minute Walk Test. Studies shown assess 6-Minute Walk Test in children [64, 68, 76] and adults [48, 68, 71, 73, 85]. Data are presented as distance walked (*darker colors*) and/or percent predicted distance walked (*lighter colors*) depending on data availability. Follow-up times varied as indicated: Whyte et al. 2016—5 years; Padidela et al. 2025—3 months; Kishnani et al. 2019—5 years; Kishnani et al. 2024—1 year; Genest et al. 2020—1 year; Seefried et al. 2023—1 year; Moss et al. in preparation—3 years. [a]Kishnani, et al. 2019 reports data from 6 adolescents aged 13 to < 18 years and 13 adults aged ≥ 18 years

HPP [13, 15]. Infants (n = 5) who started asfotase alfa treatment shortly after birth lost fewer primary teeth prematurely than preschool-aged children (n = 6) who were treatment-naive at the time of assessment (mean 1.8 vs. 10.2 teeth) [72]. Individual case studies also suggest that asfotase alfa slows the rate of premature tooth loss and reduces premature tooth mobility in children, supporting the effects on tooth stabilization and suggesting improved mineralization [83, 84].

Physical Function

Children and adults with HPP often have poor physical function that may stem in part from muscle weakness and fatigue. Studies using the 6-Minute Walk Test (6MWT), which is a validated measure of walking fatiguability [45], demonstrate the efficacy of asfotase alfa in improving physical performance in children with HPP (Fig. 3). In an open-label trial in children 6–12 years of age, asfotase alfa treatment significantly improved the percent predicted distance walked by 36% at 5 years of follow-up, with 78% (7/9) of children performing in the normal range [64]. In a real-world analysis of 6MWT data from children ≥ 5 years of age, median distance walked improved by approximately 110.0 m after 3 months of treatment, and improvements were sustained throughout 4.5 years of follow-up [76]. Children in this analysis also maintained modified Bleck scores close to 9 throughout follow-up [76]. The Bleck scoring scale measures mobility, and a score of 9 is the highest score on the scale, corresponding to community walkers who do not use canes or crutches [47]. Similar findings were reported in a case series of patients with HPP, in which 2 children had 52 m mean improvements in 6MWT distance walked after starting asfotase alfa treatment [83], exceeding the minimum clinically important difference (MCID) of 20–31 m in children (Supplementary Table S1) [45]. MCIDs throughout this review are reported based on published literature as a single value if only one reference is available in the reviewed literature or as a range if multiple references are available. Not all MCIDs are established in the HPP population, as described in Supplementary Table S1.

A wide variety of clinical assessments of physical function demonstrate the clinical benefit of asfotase alfa treatment among adults and adolescents. In a randomized control trial, adults treated with asfotase alfa achieved a median 35-m improvement in 6MWT distance walked after 6 months of treatment, exceeding the MCID of 23–31 m in adults (Fig. 3; Supplementary Table S1) [45, 68]. Patients enrolled in the Global HPP Registry had mean 93 m, 62 m, and 45 m improvements in distance walked after 12, 24, and 36 months of treatment, respectively [85]. In an additional real-world analysis, the percent predicted distance walked improved by a median of 31% after 6 months of asfotase alfa treatment [48]. Adults in this analysis also achieved a median 2.0-point improvement in modified Bleck score after 36 months of treatment, with no patient experiencing a decrease in Bleck score throughout follow-up [48]. In other studies, improvements in 6MWT performance were accompanied by decreased use of assistive devices (e.g., canes, walkers). Among 10 patients who had documented use of assistive devices for the 6MWT before starting asfotase alfa treatment, 6 were able to discontinue the use of assistive devices for the test after treatment initiation [68, 71].

A retrospective analysis of medical records from 14 adults treated with asfotase alfa in routine clinical practice reported improvements in several functional outcomes after 12 months of treatment [71]. Median distance walked on the 6MWT significantly improved by 53 m [45, 71], and median time to complete the Timed Up-and-Go (TUG) test improved by 3.1 s (MCID range of 0.8–1.4 s; Supplementary Table S1) [71]. Asfotase alfa also significantly improved outcomes in the gait speed test and repeated Chair-Rise Test (CRT), both of which are components of the Short Physical Performance Battery physical function test. Median speed to walk 4 m increased by 0.3 m/s at 12 months of treatment (MCID range of 0.03–0.13 m/s; Supplementary Table S1), and 3 of 4 patients no longer needed assistive devices to complete the test after 6 months of treatment. Median time to complete the CRT improved by 9.2 s (MCID

2.3 s; Supplementary Table S1), and median Lower Extremity Functional Scale (LEFS) score significantly improved by 29 points (out of a maximum score of 80, MCID range of 9–12.5 points; Supplementary Table S1) [41, 71]. For each of these outcomes, results were sustained throughout an additional year of follow-up [73]. Further, the median urinary PEA/creatinine ratio in these patients significantly decreased from 53.2 mmol/mol creatinine at baseline to near-normal levels within 6 months of asfotase alfa treatment, with levels consistently reduced for up to 24 months of follow-up [29]. These results may suggest the correction of PEA accumulation, which is a hallmark of ALP deficiency. A randomized study further corroborated an improvement in LEFS in 13 patients receiving asfotase alfa [68]. Four of these patients receiving asfotase alfa had clinically meaningful (≥ 9-point increases) improvements in LEFS scores after 6 months of treatment, and 7 of 18 patients had clinically meaningful improvements at last follow-up [68]. Furthermore, the improvements in LEFS were accompanied by increased bone mineralization, as measured by transiliac bone biopsy.

Motor Function

Asfotase alfa treatment also improves HPP-related motor dysfunction. Among children enrolled in the Global HPP Registry, almost 20% have gross motor delays, with nearly all infants and young children with HPP experiencing this motor dysfunction [6, 13, 67]. In a clinical trial in children ≤ 3 years of age at baseline, asfotase alfa treatment improved median gross motor scores in the Bayley Scales of Infant and Toddler Development, version 3 (BSID-III) assessment by 5.0 points out of a total maximum score of 72 points after 3 years (MCID 5 points; Supplementary Table S1) [53, 67]. Median fine motor and cognitive scores on the BSID-III assessment also improved by 4.0 and 7.0 points, respectively, indicating function in the normal range after 3 years. As children in this study aged throughout follow-up, they progressed to the Peabody Developmental Motor Scales, second edition (PDMS-2) and the Bruininks–Oseretsky Test of Motor Proficiency, second edition (BOT-2) assessments of motor function. Five of seven children with PDMS-2 scores > 1 standard deviation below normal at baseline improved to within 1 standard deviation of normal. Although patients had been treated with asfotase alfa for 5 years at the time of their first BOT-2 assessment, all 6 patients who completed more than one test showed increased age-equivalent scores, with 3 achieving scores within the normal range by the end of the study [67].

An independent clinical trial in children 6–12 years of age showed that 5 years of asfotase alfa treatment led to an 18-point significant improvement in the median BOT-2 score, with median scores in the normal range after 1 year of treatment [64]. In a randomized study in patients 13–65 years of age with HPP, 6 months of treatment with asfotase alfa led to a 4-point increase in the running speed and agility subtest and a 3-point improvement in the strength subtest of BOT-2; these results were sustained throughout 5 years of follow-up [68]. Finally, motor function was assessed using the Brief Assessment of Motor Function (BAMF) in a real-world analysis of patients younger than 4 years of age. Results showed a median 7.0-point improvement in scores for the lower and upper extremity function assessments after 36 months of asfotase alfa treatment [76].

Muscle weakness, a potential contributor to physical and motor dysfunction in patients with HPP, is reported by 13% of children and 31% of adults enrolled in the Global HPP Registry [1]. While muscle weakness in HPP could potentially arise from the significant interplay between bone and muscle strength or osteomalacia [86, 87], results of preclinical studies suggest that mitochondrial dysfunction may substantially contribute to muscle weakness in HPP. A mouse model of HPP showed reduced spare respiratory capacity, a measure of the cellular ability to respond to increased energy demands, in muscle fiber bundles relative to wild-type mice, suggesting altered mitochondrial bioenergetics in the absence of skeletal manifestations [32, 88]. Further perturbations in mitochondrial metabolism and mitochondrial ultrastructure have also been reported in other mouse and sheep models of

HPP [89–91]. Further investigation of the mechanism underlying muscle weakness in HPP, its potential association with physical functionality, and the effects of ERT are warranted.

Pain and Disability

Physical and motor dysfunction are often accompanied by pain, which is commonly reported in patients with HPP, with nearly a quarter of children and approximately three-quarters of adults reporting any form of pain [1, 15]. In a clinical trial of 13 children aged 6–12 years, median pain score decreased by 20 points and median disability score decreased by 1 point on the Child Health Assessment Questionnaire. Median scores were 0 for both metrics after 5 years of asfotase alfa treatment, indicating no pain or disability [64]. The Pediatric Outcomes Data Collection Instrument (PODCI) global function median score significantly improved by 25 points out of a maximum score of 100 after 5 years of treatment in this cohort (MCID range of 3.8–7.3 points; Supplementary Table S1) [58, 64]. Among children taking analgesics, 54% (7/13) stopped all analgesics after up to 5 years of treatment with asfotase alfa and none were taking opioids at last follow-up [76].

Several studies have reported that asfotase alfa treatment reduces pain as measured by the Brief Pain Inventory-Short Form (BPI-SF) among adults with HPP [20, 48, 68, 85]. Median aggregate BPI-SF scores improved by 3.5–3.6 points out of a maximum score of 10 after up to 5 years of asfotase alfa treatment [48, 59, 68]. Pain severity and interference scores improved by up to 1.1 points and 1.5 points, respectively, among adults throughout 36 months of asfotase alfa treatment (MCID range of 1.0–2.16 for pain severity, 0.4–2.3 points for pain interference; Supplementary Table S1) [85]. Worst pain in the past 24 h similarly improved by up to 1.7 points. In the same analysis, the proportion of patients who reported no disability, as measured by the Health Assessment Questionnaire-Disability Index, increased from 9% (n = 5) at baseline to 18% (n = 11) at month 36 [85]. Two analyses that assessed pain in adults using a 10-point Likert scale showed either no change or a 1-point improvement in pain scores through up to 2 years of treatment [71, 73]. Two studies reporting analgesic use in adults treated with asfotase alfa show conflicting results, with one study reporting a 50% decrease in patients using analgesics after 1 year and the other reporting a 60% increase after up to 5 years [48, 75]. In the latter study, 33% (8/24) of patients discontinued at least one opioid during follow-up, with 4 of these patients discontinuing all opioid medications [48]. Finally, an independent analysis showed that 33% (4/12) of adults reduced use of pain medications from daily to on demand [71]. In a recent case study, a woman with HPP who reported burning pain in her lower extremities had complete relief of symptoms after 9 months of asfotase alfa treatment, suggesting improvement of neuropathy [92].

Health-Related QoL

Bone hypomineralization, physical and motor dysfunction, chronic pain, and disability experienced by children and adults with HPP are among the many factors leading to reduced QoL in patients with HPP measured with several tests [13, 15]. The effect of asfotase alfa treatment on QoL in children with HPP was assessed in one study using the Pediatric Quality of Life Inventory (PedsQL) survey, which showed that the median PedsQL score among 20 children improved by 21.7 points on a 100-point scale after 5 years of asfotase alfa treatment [60, 76]. The MCID for the PedsQL survey is 4.4 points (Supplementary Table S1).

The impact of asfotase alfa treatment on QoL in adults with HPP was assessed in three studies using the 36-item Short Form Health Survey (SF-36v2), in which patients reported poorer median Physical Component Summary scores than the survey-defined US population score of 50 before starting asfotase alfa treatment [71, 73, 85]. Physical Component Summary scores improved by approximately 5 points after 6 months of asfotase alfa treatment [85], and results were further improved or sustained for up to 36 months (Fig. 4) [71, 73, 85]. The MCID range for Physical Component Summary score is 2–7 points, with several studies listing 5 points as clinically

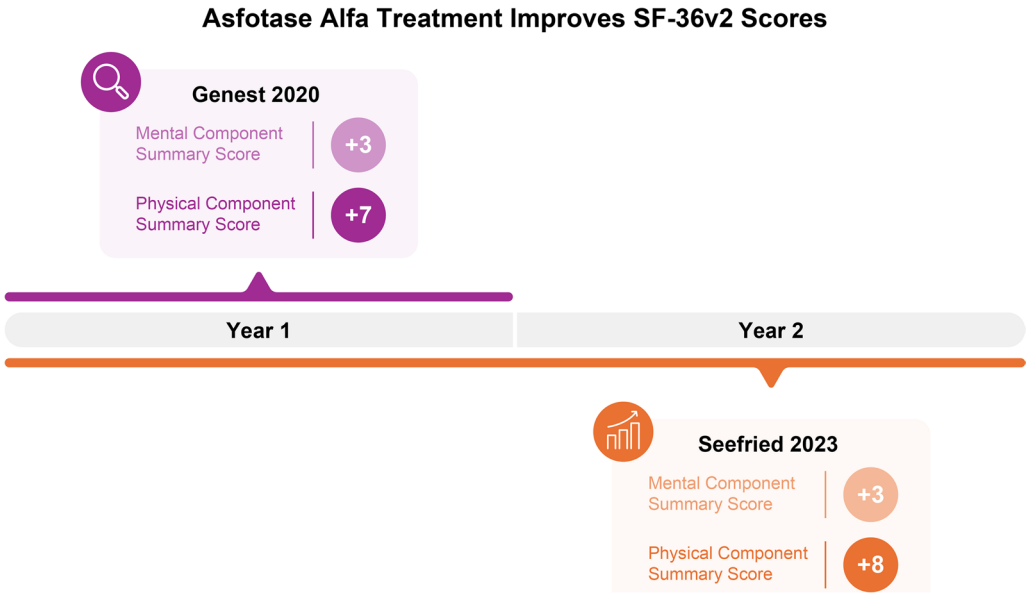


Fig. 4 Asfotase alfa treatment improves SF-36v2 scores. Studies show improvements in Mental and Physical Component Summary scores in patients in the observational EmPATHY study after up to 2 years of follow-up [71, 73]

important (Supplementary Table S1). Baseline Mental Component Summary scores across studies were similar to or below that of the general US population and increased by approximately 3–6 points with asfotase alfa treatment (MCID range 2.5–6.3 points; Supplementary Table S1) [71, 73, 85]. An additional study assessed QoL in adults with the EQ-5D-3L survey, which has a maximum score of 1.0 indicating perfect health. Median scores among 24 adults improved by 0.15 after 6 months of treatment and 0.39 after 36 months (MCID range of 0.04–0.1 points; Supplementary Table S1) [48]. A recent publication assessed additional health-related QoL outcomes among adults with HPP. After 1 year of asfotase alfa treatment, 66% fewer adults reported moderately severe depression, 65% fewer reported presenteeism, and no patients reported absenteeism as measured using the Patient Health Questionnaire-9 and Work Productivity and Activity Impairment Questionnaire: Specific Health Problem surveys [75]. High proportions of patients also reported treatment satisfaction (72%) and responded favorably when asked whether they thought that treatment with asfotase alfa was good for them (93%) per the Treatment Satisfaction with Medications Questionnaire [75].

Safety

The safety of asfotase alfa has been rigorously documented throughout the clinical trials and real-world analyses cited above. Asfotase alfa treatment is well tolerated in both children and adults. The most commonly reported adverse event for patients of all ages is injection-site reactions with transient erythema or pyrexia [6, 64, 65, 67–71, 73, 74]. Of note, some patients have experienced hypersensitivity reactions or lipodystrophy after injection [67, 68, 70, 71, 73, 74]. Accordingly, the Strensiq US prescribing information lists each of these events as occurring in ≥ 10% of treated patients [7]. Ectopic calcifications have been reported in ≥ 10% of treated patients; however, ectopic calcifications are also a well-documented feature of HPP among patients who are not treated with ERT [7, 93].

Discontinuation

Evidence on the effects of asfotase alfa discontinuation or interruption are sparse but generally

support that treatment interruption can lead to a return of clinically significant manifestations. The occurrence of seizures was tied to asfotase alfa treatment status in a patient who started asfotase alfa treatment at postnatal day 2, with seizures ceasing after treatment start, returning after interruption, and ceasing again after reinitiation [78]. In a patient who started asfotase alfa treatment at age 4 months, treatment discontinuation at age 6 years led to hypercalcemia, seizures, severe nausea and vomiting, and death [94]. Among 5 adults with HPP, 4 patients had worsening pain after interruption of asfotase alfa treatment [95]. Pain improved after reinitiation of treatment, although 3 patients reported that pain had a higher impact on QoL after reinitiating treatment [95].

DISCUSSION

The accumulated evidence from clinical trials and real-world evidence analyses described in this review consistently demonstrate the efficacy and effectiveness of asfotase alfa in improving both skeletal and nonskeletal manifestations of HPP, including physical and motor function, which may stem in part from muscle weakness. Since its first approval 10 years ago, a sizeable population of patients has been treated with asfotase alfa, increasing survival of infants and reducing disease burden and improving QoL among children, adolescents and adults with HPP. The Global HPP Registry began enrolling patients in 2015, and, as of November 2024, 636 (42%) of the 1520 patients enrolled in the Registry have been treated with asfotase alfa, creating a large pool of data to further assess clinical effectiveness and safety of ERT. Further, outcomes of assessments used in real-world analyses, including analyses of the Global HPP Registry, have reshaped the way we think about HPP burden, diagnosis, and treatment [25, 26, 81, 85].

The range of clinical endpoints used to investigate HPP disease burden and clinical efficacy of asfotase alfa varies greatly between studies, but similar and consistent patterns are observed. The efficacy of asfotase alfa in improving bone mineralization is determined by examining the changes in radiographs before and after treatment. Similarly, radiographic data are used to identify pseudofractures and fractures, including atypical femoral fractures and metatarsal fractures that are prevalent among adults with HPP [96], and to document the healing of these fractures/pseudofractures after initiation of ERT. However, radiographic assessments of the effects of ERT on fracture healing are mostly subjective and lack precise quantification of skeletal changes over time. Recent efforts have been made to develop a graded scoring scale with the potential to semi-quantify the effect of ERT on pseudofracture healing. The 4B Scale, which refers the 4 stages of pseudofracture healing (Breach–Beak–Bump–Bridge), serves as a model to identify and characterize pseudofractures and may potentially be used to document pseudofracture healing throughout ERT treatment [97]. An additional method for quantifying disorganized bone components on X-ray images has also been reported [98].

Other measures to assess the effect of ERT on skeletal signs include RGI-C and RSS, which are often used in children with open growth plates [6, 14, 64, 67]. However, the use of RGI-C is not generalizable given that it requires special expertise to administer [42]. The RGI-C was validated against the RSS [42], which may be more readily adopted into clinical practice. Use of dual-energy X-ray absorptiometry is not recommended in HPP to either confirm the diagnosis or to quantify disease burden because this measure fails to discriminate between osteomalacia, a hallmark of HPP, and osteoporosis, and bone mineral density scores are typically within or above the normal range [16, 96, 99]. Other imaging modalities, such as magnetic resonance imaging and high-resolution computed tomography, could be useful future tools to assess bone marrow edema, bone structure, and the effect of ERT on bone pathology in patients with HPP [18, 100].

Several measures are used to assess the nonskeletal effects of ERT in HPP, including assessing changes in muscle weakness, which can be observed in the absence of skeletal manifestations [25]. The physical and motor dysfunction reported in patients with HPP can be associated

with chronic musculoskeletal pain and reduced QoL. In patients who are mobile, the CRT, TUG test, 6MWT, and LEFS are measures that effectively assess fatiguability, mobility, and strength, and improvement in the scores on these tests may be used as markers of ERT efficacy/effectiveness in reducing HPP disease burden [41, 45, 49]. The CRT measures how long it takes an individual to perform 5 repeated sit-to-stands from a standard-sized chair and provides data on muscle strength of the proximal thigh muscles [50, 51]. The test takes only seconds to complete [50]. Another version of the CRT measures how many sit-to-stands an individual can achieve in 30 s [101]. While this 30-s sit-to-stand test has not been used in patients with HPP, the method offers similar clinical utility to the CRT and may be used to assess a wide variety of physical ability levels. The TUG test records the time to stand up from a seated position, walk 3 m, turn, walk back, and return to a seated position [49]. Like the CRT, the TUG can be completed in seconds. The 6MWT is a validated test, the results of which have been shown to correlate with changes in other measures of physical function in HPP, such as LEFS, PODCI, and BPI-SF [45], and, as a result, serves as a valuable indicator of overall disease burden in patients with HPP. Shorter distances walked on the 6MWT test are also correlated with higher mortality in older adults [102]. The 6MWT has been used in combination with LEFS in clinical trials and in real-world analyses in patients with HPP [68, 71, 73]. Among children, distance walked in the 6MWT also correlates with scores on the modified Performance-Oriented Mobility Assessment-Gait (mPOMA-G) test. mPOMA-G is designed to measure gait impairment in children who are mobile and has been validated in children with HPP [103]. To date, no clinical trials or real-world analyses have evaluated the impact of asfotase alfa on mPOMA-G scores. Impairment in bone mineralization and the resulting physical and motor dysfunction culminate in chronic pain and reduced QoL, both of which can be improved by ERT, and these improvements can be measured using several tests in the form of questionnaires including SF-36v2 and EQ-5D-3L in adults or PedsQL in children with HPP. Asfotase alfa improves scores in these and other surveys, corresponding with improvements in radiographic and functional outcomes [48, 71, 73, 75, 76, 85].

This review has some limitations. Because HPP is a rare disease with potentially lethal outcomes, there are relatively few randomized control studies to establish asfotase alfa clinical efficacy. Randomized studies to assess asfotase alfa efficacy have also enrolled small numbers of patients, again in line with HPP being a rare disease. At present, data showing the effects of asfotase alfa on fracture healing and dental outcomes are limited to small observational studies or case studies. Illustrative case studies describing the effects of asfotase alfa on these outcomes were included in this review, although other case studies were excluded if data could instead be reported from larger studies. Finally, HPP does not have an ICD-10 code, which makes evaluation of claims and electronic medical records challenging and could lead to a paucity of data.

FUTURE DIRECTIONS

This review highlights robust evidence on the clinical efficacy and safety of asfotase alfa in improving skeletal and nonskeletal manifestations in pediatric and adult patients with HPP. HPP is a systemic disease that can affect other tissues and organs beyond the skeleton. The physical and motor dysfunction observed in many patients with HPP may stem from muscle weakness and fatigue. Data from preclinical models suggest that muscle weakness in HPP may be due in part to mitochondrial dysfunction independent of impaired skeletal mineralization or reduced oxidative phosphorylation and ATP synthesis [32, 91, 104]. Although it remains to be determined whether mitochondrial dysfunction is a PLP-mediated phenomenon, it is noteworthy that intracellular PLP is a cofactor in over 140 enzymatic reactions throughout the body, potentially contributing to nonskeletal manifestations of HPP [105].

Data derived from clinical trials and real-world analyses of asfotase alfa efficacy over the past 10 years are encouraging, creating a foundation for further improvement in the understanding of HPP pathology. Future research is needed

on novel bone imaging technologies, which may allow for easier quantification of bone pathology in HPP [98]. In addition, more research is required to set MCIDs for clinical assessments in HPP to fully characterize the potential benefits of ERT. The long-term safety, sustained clinical efficacy, and well-characterized repertoire of clinical assessments used to evaluate asfotase alfa support the investigation of efzimfotase alfa, a novel ALP ERT currently in development [106].

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Data Availability. Alexion, AstraZeneca Rare Disease will consider requests for disclosure of clinical study participant-level data provided that participant privacy is assured through methods like data de-identification, pseudonymization, or anonymization (as required by applicable law), and if such disclosure was included in the relevant study informed consent form or similar documentation. Qualified academic investigators may request participant-level clinical data and supporting documents (statistical analysis plan and protocol) pertaining to Alexion-sponsored studies. Further details regarding data availability and instructions for requesting information are available in the Alexion Clinical Trials Disclosure and Transparency Policy at https://www.alexionclinicaltrialtransparency.com/data-requests/.

Declarations

Conflict of Interest. Aliya A. Khan has received honoraria from Amgen and Alexion and support from Ascendis, Calcilytix, Amolyt, and Alexion, AstraZeneca Rare Disease. Eric T. Rush has received consulting fees, support for attending meetings, and honoraria from Alexion, AstraZeneca Rare Disease. He is also on the Alexion advisory board and his institution has received grants from Alexion, AstraZeneca Rare Disease. Craig Wakeford and Daniel Staub are employees of and may own stock/options in Alexion, AstraZeneca Rare Disease. Maria Luisa Brandi has received consulting fees, support for attending meetings, and honoraria from Alexion, AstraZeneca Rare Disease. She is also on the Alexion advisory board and her institution has received grants from Alexion, AstraZeneca Rare Disease.

Ethical Approval. This review article did not require institutional review board or institutional animal care and use committee approval, as it is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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