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INVITED REVIEW

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Enzyme replacement therapy for hypophosphatasia—The current paradigm

Aaron Schindeler[1,2] | Karissa Ludwig[3,4] | Craig F. Munns[3,4]

[1]Bioengineering and Molecular Medicine Laboratory, The Children's Hospital at Westmead and Westmead Institute for Medical Research, Westmead, New South Wales, Australia

[2]Children's Hospital at Westmead Clinical School, University of Sydney, Camperdown, New South Wales, Australia

[3]Child Health Research Centre and Faculty of Medicine, The University of Queensland, Brisbane, Queensland, Australia

[4]Department of Endocrinology, Queensland Children's Hospital, Brisbane, Queensland, Australia

Correspondence
Craig F. Munns, Child Health Research Centre and Faculty of Medicine, The University of Queensland, Brisbane, Queensland, Australia.
Email: c.munns@uq.edu.au

Abstract

Hypophosphatasia (HPP) is a rare, inherited, and systemic disorder characterized by impaired skeletal mineralization and low tissue nonspecific serum alkaline phosphatase (TNSALP) activity. It is caused by either autosomal recessive or dominant-negative mutations in the gene that encodes TNSALP. The phenotype of HPP is very broad including abnormal bone mineralization, disturbances of calcium and phosphate metabolism, pain, recurrent fracture, short stature, respiratory impairment, developmental delay, tooth loss, seizures, and premature death. Other than supportive care, there has been no disease-specific treatment available for those with HPP. Asfotase alfa is a fully humanized, recombinant enzyme replacement therapy for the management of HPP. It is available in several countries for the treatment of the more severe forms of HPP, namely perinatal and infantile HPP. This review will summarize the preclinical data on asfotase alfa and highlight the data from clinical trials and case reports. These data show the transformative nature of asfotase alfa when administered as part of an interdisciplinary treatment model.

KEYWORDS

asfotase alfa, enzyme replacement therapy, HPP, hypophosphatasia, strensiq

1 | HYPOPHOSPHATASIA—ETIOLOGY, DIAGNOSIS, CLASSIFICATION AND PATHOGENESIS

Hypophosphatasia (HPP) is a genetic disorder with a variable skeletal and extra-skeletal phenotype that is associated with an underlying deficiency in serum alkaline phosphatase (ALP). HPP is most widely recognized for its association with a range of skeletal features, including osteomalacia and rickets, fractures, and bone pain, as well as near-universal challenges with dental health in affected individuals. HPP results from loss-of-function mutations in the ALPL gene, that encodes for tissue-nonspecific alkaline phosphatase (TNSALP). *ALPL* is highly expressed in the skeleton, liver, kidney, and developing teeth and is distinct from *ALPI*, *ALPP*, and *ALPPL2*, which express alkaline phosphatases in the intestine, placenta, and germ cells. While TNSALP has a range of substrates, several key targets become upregulated in HPP, such as inorganic pyrophosphate (PPi), phosphoethanolamine (PEA), and pyridoxal 5'-phosphate (PLP or vitamin B6). These can serve as more specific biomarkers than low serum ALP for diagnostic purposes.

Diagnosis of HPP is typically made based on a combination of clinical history, radiographic imaging, physical examination, and biochemical testing. In particular, a low serum ALP level can help distinguish it from alternative conditions with a similar presentation, such as rickets or osteogenesis imperfecta. However, biochemical testing for elevated PPi, PEA and, PLP and/or genetic testing for ALPL gene mutations is necessary to confirm a diagnosis. Notably, a

TABLE 1 Presenting respiratory, signs, symptoms, and complications in infants less than 6 months of age.[4]

Manifestation	Observed incidence % (n = 48)
Chest deformity	80%
Respiratory distress	64%
Decreased oxygen saturation	53%
Tachypnoea	53%
Respiratory failure	47%
Respiratory tract infection	42%
Pneumonia	18%

wide range of loss of function mutations (over 300) have already been linked to HPP.[1] In the case of early onset disease— particularly when skeletal anomalies are first detected in utero—there can be significant diagnostic challenges. Differential diagnoses include osteogenesis imperfecta, campomelic dysplasia, cleidocranial dysplasia, thanatophorhic dysplasia, and achondrogenesis or hypochondrogenesis; however, prudent and expert radiological assessment can greatly assist with correct, early diagnosis.[2]

Another emerging issue is that alkaline phosphatase levels below age- and sex-specific reference ranges are not always highlighted by pathology laboratories. This can lead to a clinician failing to note and act upon the abnormal result. In a study by Deeb et al. (2018), biochemistry results from 2890 patients aged <18 were screened for low ALP levels and identified 226 with values below age and sex-specific references.[3] Eight patients were noted to have presented with features consistent with HPP, suggesting that HPP may be under-recognized.

Classification of HPP is largely governed by the age of onset of signs and symptoms, with more severe forms of the disease typically presenting earlier in life. *Perinatal HPP* is the most severe form of HPP and has onset of signs and symptoms in utero or at birth and features skeletal deformities including deformed and shortened extremities, fractures, rickets, short stature and craniosynostosis. Respiratory features are common in infants with HPP (Table 1), leading to a poor prognosis with 75% mortality by 18 months of age.[4] Infants can have a disturbance of mineral homoeostasis with hypercalcemia and hypercalciuria leading to nephrocalcinosis. Vitamin B6-dependent seizures are seen in approximately 17% of infants with HPP and are associated with a 60% increased relative risk of mortality.[4] Gross motor delay is common. A rare subset of neonates with *Benign Perinatal HPP* show a spontaneous improvement after birth but may have some persistent features of hypophosphatasia. *Infantile-onset HPP* manifests in the first 6 months of life with skeletal and extra-skeletal features similar to those with Perinatal HPP, but typically less severe. *Childhood-onset HPP* appears after the first 6 months and often presents with gross motor delay (89%) including delayed walking (24%).[5] Radiological rickets (83%) is common, as are lower limb deformity, chronic skeletal pain, and short stature, along with recurrent fractures (23%). Premature tooth loss (before the age of 5 years) with roots intact is a hallmark feature of HPP due to reduced mineralization of acellular cementum.[5] Adults with HPP can also experience exfoliation of secondary dentition. Odontohypophosphatasia (*OdontoHPP*) occurs in early childhood and chiefly features premature tooth loss with limited impact on the skeleton. Finally, *Adult-onset HPP* typically shows milder symptoms than earlier onset variants of the condition but can be associated with bone pain, fragility, and stress fractures alongside delayed fracture healing, and osteomalacia. These features are not exhaustive, and there is variation in presentation and phenotypic overlap with other skeletal conditions.[4]

TNSALP is expressed by osteoblasts and hypertrophic chondrocytes and is necessary for the dephosphorylation of PPi to form inorganic phosphate and the growth of hydroxyapatite crystals that are essential for bone mineralization. Overexpression of TNSALP can lead to overactive bone remodelling, as is seen in Paget's disease and some instances of osteomalacia, and certain bone metastases. Low TNSALP can be caused by genetic mutations (i.e., HPP) but can also result from malnutrition and/or deficiencies in copper or magnesium. In HPP, low TNSALP is associated with a fundamental disruption in mineral homoeostasis and excessive levels of PPi. Elevated PPi itself inhibits hydroxyapatite formation but can also lead to calcium pyrophosphate dihydrate depositions as well as calcific periarthritis and ligament calcification seen in some cases of HPP. The inhibition of normal bone mineralization from raised PPi can also result in raised circulating calcium and phosphate levels and subsequent reduction in parathyroid hormone expression.

Extra-skeletal features of HPP including muscle weakness and seizures can be independent of excess PPi and hypomineralization. Clinical presentations of HPP feature impaired physical function[6] and a recent examination of the *Alpl*$^{-/-}$ mice revealed reduced muscle size, muscle mitochondrial function, and fibre type proportion.[7] This weakness is likely influenced by indirect factors such as bone deformity and inactivity following fracture, but other mechanisms may be relevant. For example, it has been postulated PPi may directly impair muscle based on studies showing that PPi analogues like etidronate can affect muscle weakness.[1] Elevated PLP may also impact neuromuscular function. The seizures that affect more severe HPP cases are often linked to defects in pyridoxal metabolism. Systemic TNSALP dephosphorylates PLP (vitamin B6) into pyridoxal, allowing it to cross the plasma membrane into the central nervous system (CVS). Once pyridoxal has crossed into the CVS, it is re-phosphorylated into PLP. A deficiency of TNSALP leads to a deficiency of PLP in the CVS and seizures. This is supported by data from *Alpl*$^{-/-}$ mice, where lethal seizures can be rescued by pyridoxal dosing,[8] although mice still develop a dental phenotype.

2 | PRECLINICAL DEVELOPMENT OF AN ENZYME REPLACEMENT STRATEGY

In 2008, Millán et al. published a study examining rescue of the *Alpl*$^{-/-}$ knockout mouse line (also referred to in the literature as *Akp2*$^{-/-}$, TNALP-null, and TNSALP-knockout mice). An engineered human TNSALP featuring a human IgG Fc region and a deca-aspartate (D_{10}) motif, termed sALP-FcD_{10}, was produced as a purified recombinant protein. Enzyme

replacement by subcutaneous injection led to reliable rescue at a range of doses.[9] Further testing was conducted using this mouse model[10] to determine the ED_{80} (the dose preventing bone defects in 80% of mice), which ranged between 2.8 and 3.2 mg/kg/day for different skeletal sites. This study also featured more detailed radiographic, microCT and histomorphometric data. The agent was renamed from sALP-FcD_{10} to ENB-0040, although it later became referred to as asfotase alfa and commercially under the brand name Strensiq®.

While these studies led to clinical trials, murine studies with asfotase alfa have continued. A 2017 study focused on cranial base abnormalities with parallels to the craniosynostosis seen in severe forms of HPP.[11] This study focused on the importance of TNSALP in chondrocytes including chondrocyte apoptosis and endochondral ossification. These cartilage-associated phenotypic manifestations were rescuable by asfotase alfa. A 2023 study has recently attempted perinatal therapy, an intervention that has not yet been trialled in humans.[12] Pregnant dams were dosed with asfotase alfa, as were newborns from birth, with outcomes measured at postnatal day 20. Data suggested improved results from such early intervention, with particular benefit for the maxillofacial region including the teeth.

Asfotase alfa has also been used in to treat mouse models of neurofibromatosis type 1 (NF1) affected bone.[13] NF1 is a genetic disorder that features nerve-associated tumour formation, but also presents with focal bone dysplasias and systemic hypomineralization and increased cortical porosity. NF1 mutations lead to the enhancement of Ras-MAPK signalling, which can impact on osteoblast expression of enzymes involved with mineral homoeostasis. Asfotase alfa treatment improved bone measures in $Nf1_{Col2}^{-/-}$ and $Nf1_{Osx}^{-/-}$ mice that lacked *Nf1* expression in their chondroprogenitors and/or osteoprogenitors. This study also featured in vitro experiments using bone marrow stromal cells isolated from orthopaedic NF1 patients.

Finally, two recent papers have examined the delivery of a TNSALP-D_{10} enzyme replacement therapy, not by injection of recombinant protein, but rather by a gene therapy approach.[14,15] Both studies employ an adeno-associated viral vector; the AAV8 serotype is used due to its proven efficacy in mouse models, however alternative packaging would likely be needed for clinical use in humans. A dose of 3×10^{11} vg/mouse was sufficient to elevate serum ALP activity and extend the lifespan of $Alpl^{-/-}$ mice[14] and similar yield bone improvements in the limb-targeted $Alpl_{Prx1}^{-/-}$ mice and $Phospho1^{-/-}$ model of pseudo-HPP.[15] While there may be cost and convenience benefits to a one-time gene therapy intervention, this technology still holds a host of technical and practical limitations. A notable constraint is the ability to modulate ALP dose following a gene therapy intervention, whereas a clinical dose of asfotase alfa has the potential to be modulated in response to patient needs.

3 | CLINICAL TRIAL FINDINGS

The first published case report for HPP enzyme replacement was a 2012 paper concerning an infant with perinatal lethal HPP on mechanical ventilation.[16] ENB-0040 (asfotase alfa) was given, and the infant showed a steady increase in lung function and a decrease in ventilator dependency. However, over the past 12 years, there have been numerous registered paediatric and adult clinical trials (see Table 2, sourced from clinicaltrials. gov).

Key findings have been published in a series of peer-reviewed research papers and illustrate the transformational impact asfotase alfa can have on the trajectory of severe disease and quality of life improvements with later onset HPP.

The first published clinical trial for asfotase alfa for HPP was linked to trial NCT00952484 and published in 2016.[17] In this Phase 2 intervention trial, patients were randomized for dose (6 mg/kg/week or 9 mg/kg/wk), and patient outcomes were compared to historical controls. 12/13 recruited patients completed the study and proceeded through to the extension phase. The study demonstrated a significant improvement in the median Radiographic Global Impression of Change (RGI-C) score within 6 weeks of initiating treatment. Growth was significantly improved after 18 months, and there were persisting benefits to parent-reported surveys of pain and disability. There were no significant adverse events, withdrawals, or deaths. While patients developed antibodies to asfotase alfa, therapeutic efficiency did not appear to be compromised.

This was followed in the same year by a parallel Phase 2 interventional study for the treatment of more severe perinatal and infantile HPP.[18] This study was linked to trial NCT00744042 and its corresponding extension, as well as NCT01176266; it also incorporated data from several HPP natural history studies. While the intervention was arguably lifesaving in some cases, only 12/21, both survived and were weaned from ventilatory support. The results of NCT01176266 featuring early onset HPP (perinatal or infantile HPP and <5 years old upon initiating treatment) were published separately in 2019.[19] This paper again indicated that asfotase alfa was well-tolerated and was impactful for treating HPP-related hypomineralization and impaired respiratory function. 2019 also saw the publication of the 7-year extension phase data to NCT00744042 (i.e., NCT01205152).[20] Infants who had remained on long-term treatment showed sustained improvements with key outcome metrics including growth, bone mineralization, and respiratory function. Notable amongst the adverse events was craniosynostosis in 7/11 patients, which was in some cases rated as severe.

Similar benefits were seen in a 13-patient Japanese cohort, although this study had a highly inclusive age range for recruitment. Amongst the most frequent adverse events were injection site reactions,[21] which remains a challenge for patients on long-term asfotase alfa. This study also highlighted incidents of hypercalcemia in a subset of infantile HPP patients that was also managed with a low-calcium and/or a low-phosphorus formula.

Several studies have addressed the pharmacokinetics and pharmacodynamics of asfotase alfa in adults with pediatric-onset HPP.[22,23] These studies examined in a clinical setting the reductions in circulating PPi and PLP markers in response to enzyme replacement at a range of doses. The data support the current recommendation of 6 mg/kg/week for this population.

A notable retrospective analysis (referring to trial NCT01163149) reported ectopic ocular calcifications in adult HPP

TABLE 2 Enzyme replacement therapy clinical trials.

ClinicalTrials.gov ID	Name	Status	Phase	# Actual enrolment	Date range	Eligibility	Study design	Ref
NCT00739505	Safety Study of Human Recombinant Tissue Nonspecific Alkaline Phosphatase Fusion Protein Asfotase Alfa in Adults With Hypophosphatasia (HPP)	Completed	Phase 1	6	2008–9	18–80 yo, clinical HPP diagnosis	Treatment, Non-Randomized, Single Group Assignment, Open Label	1
NCT00744042	Safety and Efficacy Study of Asfotase Alfa in Severely Affected Infants With Hypophosphatasia (HPP)	Completed with Results	Phase 1/2	11	2008–10	up to 36 m, severe HPP	Treatment, Single Group Assignment, Open Label	2
NCT00894075	Safety and Efficacy Study of ENB-0040 in Juvenile Patients With Hypophosphatasia (HPP)	Withdrawn	Phase 2	0	(2009–14)	5–12 yo, ambulant, history of HPP	Treatment, Single Group Assignment, Open Label	3
NCT00952484	Safety and Efficacy of Asfotase Alfa in Juvenile Patients With Hypophosphatasia (HPP)	Completed with Results	Phase 2	13	2009–10	5–12 yo, prepubescent, history of HPP	Treatment, Randomized, Parallel Assignment, Open Label	4
NCT01163149	Safety and Efficacy Study of Asfotase Alfa in Adolescents and Adults With Hypophosphatasia (HPP)	Completed with Results	Phase 2	19	2010–16	13–65 yo, clinical HPP diagnosis	Treatment, Randomized, Parallel Assignment, Open Label	5
NCT01176266	Open-Label Study of Asfotase Alfa in Infants and Children ≤ 5 Years of Age With Hypophosphatasia (HPP)	Completed with Results	Phase 2/3	69	2010–16	up to 5 yo, severe HPP (seen in first 6 m)	Treatment, Single Group Assignment, Open Label	6
NCT01203826	Extension Study of Protocol ENB-002-08 - Study of Asfotase Alfa in Infants and Young Children With Hypophosphatasia (HPP)	Completed with Results	Phase 2	12	2009–16	Long-term follow-up of ENB-006-09 (NCT00952484).	Treatment, Single Group Assignment, Open Label	7
NCT01205152	Extension Study of Protocol ENB-002-08 - Study of Asfotase Alfa in Infants and Young Children With Hypophosphatasia (HPP)	Completed with Results	Phase 2	10	2010–2016	Long-term follow-up of ENB-002-08 (NCT00744042).	Treatment, Single Group Assignment, Open Label	8
NCT02496689	Expanded Access Programme for Asfotase Alfa Treatment for Patients With Infantile- or Juvenile-onset Hypophosphatasia (HPP)	Approved for Marketing	Expanded Access	n/a	2019	Clinical diagnosis of infantile- or juvenile-onset HPP		9
NCT02531867	Post-approval Clinical Study of Asfotase Alfa Treatment for Patients With Hypophosphatasia (HPP) in Japan	Completed with Results	Phase 4	13	2015	Child - adult, completed HPPJEAP-01 protocol	Treatment, Single Group Assignment, Open Label	10
NCT02797821	Pharmacokinetic and Dose Response Study of Asfotase Alfa in Adult Patients With Paediatric-Onset Hypophosphatasia (HPP)	Completed with Results	Phase 2	27	2016–17	18+ yo, paediatric-onset HPP (<18 yo)	Treatment, Randomized, Parallel Assignment, Open Label	11

TABLE 2 (Continued)

ClinicalTrials.gov ID	Name	Status	Phase	# Actual enrolment	Date range	Eligibility	Study design	Ref
NCT03418389	Evaluate and Monitor Physical Performance of Adults Treated With Asfotase Alfa for Hypophosphatasia	Completed	Observational	23	2018–21	18+ yo, pediatric-onset HPP (<18 yo)	Cohort, Other	12
NCT04189315	Relieving Burden of Hypophosphatasia in Adults With Functional Impairment Due to Chronic Disease	Withdrawn	Phase 4	0	(2020–22)	18+ yo, pediatric-onset HPP (<18 yo)	Treatment, Randomized, Parallel Assignment, Open Label	13
NCT04195763	Patient Reported Outcomes in Adults With Pediatric-onset Hypophosphatasia Treated With Strensiq® (Asfotase Alfa)	Active, not recruiting	Observational	est. 100	2019–2024	18–99 yo, pediatric-onset HPP (<18 yo)	Cohort, Prospective	14
NCT05234567	A Prospective Sub-Study of the Global Hypophosphatasia Registry	Recruiting	Observational	est. 40	2022–28	Child - adult, pediatric-onset HPP (<18 yo)	Cohort, Prospective	15
NCT06015750	Mitigate Immune-Mediated Loss of Therapeutic Response to Asfotase Alfa (STRENSIQ®) for Hypophosphatasia	Not yet recruiting	Phase 4	est. 8	2023–27	2–18 yo with HPP, recent worsening after initial efficacy response to asfotase alfa	Treatment, Single Group Assignment, Open Label	16
NCT05890794	Pilot Trial of Single Dose Ilofotase Alfa in Hypophosphatasia	Recruiting	Phase 1/2	12	2023	18–85 yo, clinical HPP diagnosis	Treatment, Randomized, Parallel Assignment, Open Label (dose masked)	17
NCT04980248	Study of ALXN1850 in Participants With Hypophosphatasia (HPP)	Completed	Phase 1	15	2021–22	18+ yo, clinical HPP diagnosis	Basic Science, Sequential Assignment (3 sequential cohorts), Open Label	18
NCT06079281	Phase 3 Study of ALXN1850 Versus Placebo in Adolescent and Adult Participants With HPP Who Have Not Previously Been Treated With Asfotase Alfa	Not yet recruiting	Phase 3	est. 30	2023–27	2–11 yo, prepubescent, history of HPP	Treatment, Randomized, Parallel Assignment, Open Label	19
NCT06079359	Phase 3 Study of ALXN1850 in Treatment-Naïve Pediatric Participants With HPP	Not yet recruiting	Phase 3	est. 30	2024–27	2–11 yo, prepubescent, history of HPP	Treatment, Randomized, Parallel Assignment, Double Blinded	20
NCT06079372	Phase 3 Study of ALXN1850 in Pediatric Participants With HPP Previously Treated With Asfotase Alfa	Not yet recruiting	Phase 3	est. 30	2023–27	2–11 yo, prepubescent, history of HPP	Treatment, Randomized, Parallel Assignment, Open Label	21

patients who had undergone asfotase alfa treatment. This was attributed to the reductions in circulating PPi, allowing the propagation of hydroxyapatite crystals—including outside of skeletal sites. Notably, the calcifications appeared asymptomatic and did not contraindicate sustained treatment, but long-term surveillance of eye health was nonetheless encouraged.

Other key findings from published clinical trial data include improvements in physical function and quality of life following 2 years of treatment.[6,24]

4 | KEY LEARNINGS FROM CASE REPORTS

While clinical trials have informed evidenced-based interventions with asfotase alfa for HPP, there are a range of published case reports or case series that provide specific insight into unusual cases, infrequent complications, or experimental usage strategies.

Okazaki et al. intervened with asfotase alfa to treat lethal perinatal HPP from day 1 after birth.[25] Enzyme replacement led to improvements in skeletal mineralization, and the infant was able to be weaned from mechanical ventilation. With active management of calcium homoeostasis and no complications associated with craniosynostosis, the outcomes here could be considered positive. In contrast, a poorer outcome was seen in an infant with severe perinatal HPP who also commenced asfotase alfa shortly after birth (Day 6).[26] The patient developed an HPP-associated encephalopathy, despite their seizures being responsive to pyridoxine treatment. The child died at 5 months of age. Another example of a negative outcome for perinatal onset HPP was presented by Costain et al.[27] The affected child presented from birth with a severe skeletal phenotype, and ALP, PLP, and PPi levels were used to rapidly confirm a diagnosis of HPP. Substantive discussion was given on the ethical decision on whether to intervene in such a severe case, and care was given to integrating issues of bioethics, the parental wishes (including religious beliefs), and the practicalities of insurance and capacity for long-term treatment. At day six of life, a decision was made to treat with highly-specific goals of weaning the child from ventilation—a decision made by the multidisciplinary team in collaboration with the family as part of a long-term treatment plan. The infant responded poorly to treatment, and even with increased asfotase alfa dosing, there was poor chest wall growth observed. Ultimately, the enzyme replacement was ceased, and the infant died on day 100. These cases illustrate the scope of outcomes that can result when treating severe disease—even when the diagnosis and shift to enzyme replacement is rapid.

It is possible that, even for severe disease, the faster an enzyme replacement therapy can be brought online, the better for patient outcomes. A report describing the two earliest asfotase alfa treatments for HPP in Korea makes a similar speculation.[28] After 6 years, the patient who initiated asfotase alfa treatment earlier showed a better prognosis, despite initially presenting as more severe. However, many other factors could explain this observation, and more comprehensive prospective or retrospective analyses would be required to validate this association.

The use of asfotase alfa in long-term survivors of perinatal HPP is not widely reported. In one case report, a 7-year-old boy with a genetic diagnosis of HPP and showed a low serum ALP and was placed on enzyme replacement therapy to curb bone deformities, particularly bowed long bones.[29] Notably, despite an improvement in bone growth, deformity persisted; it is unclear whether this is specific to perinatal HPP, is affected by patient compliance, or related to the timing and dose.

While there are standard guidelines for asfotase alfa dosing, there is the potential for doses to be varied in response to individual patient needs. This is illustrated in a case of infantile-onset HPP, which nevertheless showed mild symptoms. A lower dose of asfotase alfa was able to provide skeletal benefits, suggesting that dose rates can be guided by clinical severity.[30]

Takagi et al. describe intervention for odontoHPP with asfotase alfa. A 2-year-old girl was diagnosed after presenting with early mobility of the deciduous teeth and was later confirmed to have an *ALPL* mutation.[31] Intervention led to a reduction in tooth mobility, but several teeth were lost prematurely shortly after starting asfotase alfa, concomitant with a common cold. It was speculated that earlier enzyme replacement therapy might be preferable. The use of asfotase alfa in odontoHPP remains controversial.

Rockman-Greenberg et al. have reported on a notable case series of six adults with HPP whose asfotase alfa treatment was discontinued. This focused on a subset of individuals in the NCT01163149 clinical trial where enzyme replacement was discontinued after 5 years for periods between 1 and 4 years.[32] The patients showed deterioration off treatment but improved once treatment restarted. These findings support the concept that enzyme replacement is a lifetime intervention. It also showed that after a period off treatment, restarting asfotase alfa remains effective. Moreover, in a pediatric setting, maintaining therapy may be important for preventing seizures.[33]

One relevant medical scenario is a later-life diagnosis of adult-onset HPP, particularly if the symptoms are mistaken for another condition including osteoporosis. This is illustrated by a case study with a 71-year-old woman with recurrent bone pain that did not respond to bisphosphonates (BPs).[34] At the time of writing the report, the patient was about to commence asfotase alfa based on a low ALP and high PEA biochemistry, although genetic testing was declined. A similar scenario was described in a 40-year-old Japanese woman who arguably had childhood symptoms consistent with HPP but only received a confirmative HPP diagnosis in later life.[35] Notably, the impetus for intervention in this case was muscle weakness and fatigue rather than the patient's skeletal concerns, and asfotase alfa provided relief for these symptoms.

One potential but rare situation is the comorbidity of HPP with another genetic condition. For example, a 38-year-old woman presented with a diagnosis of HPP as well as the connective tissue disorder, Ehler-Danlos Syndrome.[36] The authors discuss but do not report on future treatment with asfotase alfa. A female infant of

parents with hypochondroplasia was noted to have short long-bones, metaphyseal flaring and bone spurs at the midshaft fibulae on day 9 of life. She was treated with pamidronate until 28 months of age when radiographic evidence of rickets became apparent, and exome sequencing detected a heterozygous FGFR3 mutation (consistent with a hypochondroplasia phenotype) and compound heterozygous ALPL mutations. A low ALP (before pamidronate commencement) was noted retrospectively. This case again illustrates the difficulty in diagnosing HPP in the setting of a comorbid skeletal disorder, leading to inappropriate treatment.[37] The applicability of enzyme replacement therapy must consider the patient-specific manifestations when multiple conditions co-exist, particularly with respect to managing calcium and phosphate homoeostasis. Similarly, asfotase alfa can impact on other diagnostic laboratory tests. In a patient with HPP and hypogonadism, testing of testosterone values was adversely affected in immunoassays while they were on enzyme replacement therapy.[38]

Hypersensitivity to asfotase alfa is uncommon and can be at least partly mitigated by proper injection technique and injection site rotation. A 29-year-old woman with infantile-onset HPP presented having ceased asfotase alfa therapy after an episode of respiratory distress shortly after dosing.[39] She had previously taken four cycles of therapy over 3 years. The physicians designed a rapid desensitization protocol with a stepwise increasing dose. This enabled the patient to move forward with enzyme replacement therapy without further adverse events.[39]

As previously noted, asfotase alfa has shown efficacy in a mouse model of NF1 bone deficiency.[13] For challenging orthopaedic defects in an NF1 setting, such as tibial pseudarthrosis, recombinant human bone morphogenetic proteins (BMPs) and BPs have proven to be useful adjunctive agents.[40] The addition of asfotase alfa to a BMP/BP regimen was reported in a 54-year-old woman with NF1-related dystrophic scoliosis. While an isolated case, solid arthrodesis was achieved with the combination therapy.[41] Asfotase alfa has also been reviewed in the context of radiological assessment of pseudofracture repair[42] and may facilitate improved outcomes when treating HPP-related craniosynostosis.[43]

5 | TOWARDS THE FUTURE

Asfotase alfa has proven to be transformative in its capacity to improve medical outcomes and quality of life in individuals with HPP. It may be speculated that better outcomes could result from the early, rapid, and accurate diagnosis of HPP.[28] Despite early diagnosis of HPP and instigation of asfotase alfa, significant morbidity and mortality can persist. As HPP is an ultra-rare disease, it is not surprising that the diagnosis can be delayed, which can, at times, have fatal consequences. Increased awareness and education will help in reducing diagnostic delay, improving care coordination, and providing the best treatment to children and adults with HPP. This can be achieved by targeting a multi-disciplinary healthcare audience, facilitating case-based and peer-to-peer discussions among healthcare providers, and enabling optimal transition-of-care. The development of HPP centres of excellence that act as reference centres for clinical advice, research and education may be an attractive way to facilitate this (Figure 1). The involvement of consumers and international and local patient advocacy groups would be keen to the success of such centres and help greatly in all aspects of their work.

The fundamental importance of establishing multidisciplinary treatment team was highlighted by Kishnini et al. 2017, who proposed detailed international guidelines for the management of

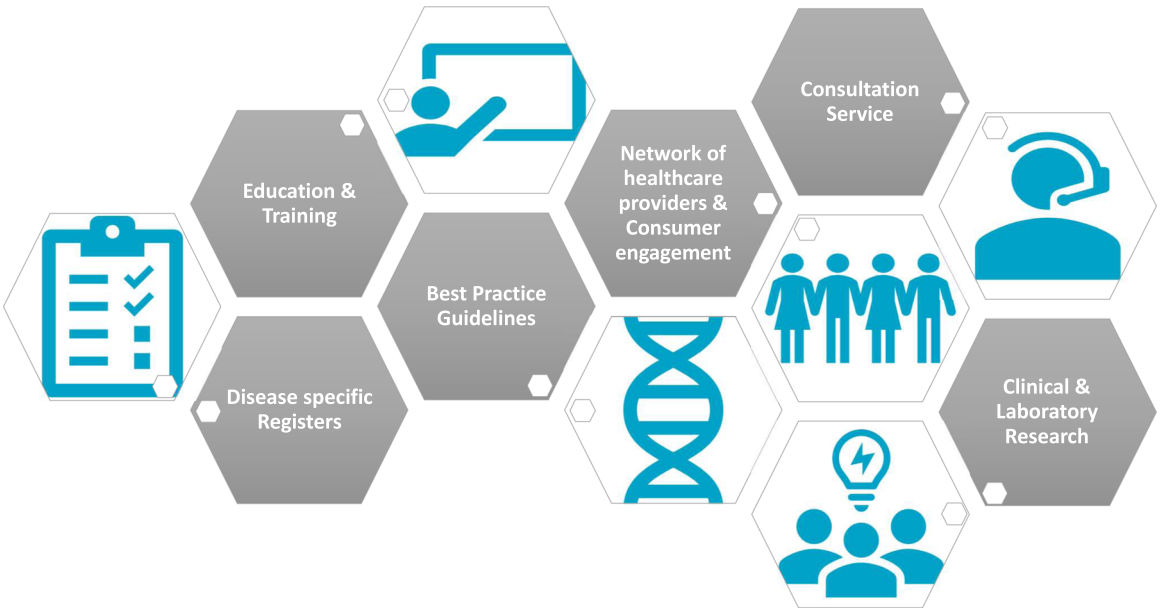

FIGURE 1 Model for HPP Centre of Excellence to facilitate clinical care, research and training. HPP, hypophosphatasia. [Color figure can be viewed at wileyonlinelibrary.com]

children and adults with HPP receiving asfotase alfa.[44] The complex, multi-system and evolving nature of HPP necessitates a core group of experienced clinicians able to call upon specialists as specific needs arise (e.g., the need for neurosurgery). Central to all care is the patient and their family. They receive close support from a clinical care coordinator, often a nurse or allied health professional.[44] With the family, the treatment team would establish the treatment goals and a detailed monitoring programme for children and adults with HPP.

The costs of enzyme replacement therapy remain substantive, limiting accessibility based on financial status and/or geographic location. It also requires accurate diagnosis, which may be currently under-identified in both children and adults. For prenatal lethal disease, there needs to be an ongoing ethical dialogue involving medical professionals and patient families regarding the realistic outcomes of treatment. Lastly, it should be noted that other enzyme replacement options may be on the horizon. Four clinical trials with an alternative enzyme replacement therapy (ALXN1850) are currently registered on clinicaltrials.gov (Table 2), for which results are pending.

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ORCID

Craig F. Munns http://orcid.org/0000-0001-5898-5808

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