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ORIGINAL RESEARCH

Mobility and Quality of Life in Adults with Paediatric-Onset Hypophosphatasia Treated with Asfotase Alfa: Results from UK Managed Access Agreement

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ABSTRACT

***Introduction*:** Hypophosphatasia (HPP) is a rare disease caused by deficient tissue–non-specific alkaline phosphatase (ALP) activity. Asfotase alfa is a tissue–non-specific ALP enzyme-replacement therapy which was reimbursed in the UK under a Managed Access Agreement (MAA). This analysis assessed safety and effectiveness of asfotase alfa in adults with HPP.

***Methods*:** This prospective, observational data collection included adults with paediatric-onset HPP enroled in the MAA and treated with asfotase alfa for ≥ 6 months to 5 years. Assessments included mobility, pain, and health-related quality of life (HRQoL), each reported at regular intervals through year 3. Analgesic use, fractures, and events of interest (EOIs) were each reported continuously throughout follow-up.

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***Results*:** Of 28 enroled treated adults, 24 were assessed for effectiveness. Distance walked in the 6-Minute Walk Test was median (min, max) 172.5 m (0.0, 380.0; *n* = 24) at baseline and improved by 157.3 m (– 171.0, 479.5; *n* = 16) at month 6; results were sustained throughout follow-up. Median (min, max) Bleck score was 6.0 (2.0, 9.0; *n* = 24) at baseline and increased to 6.5 (5.0, 9.0; *n* = 10) at month 36. Median (min, max) aggregate Brief Pain Inventory Short Form severity score was 8.0 (4.3, 10.0; *n* = 24) at baseline and improved to 4.4 (1.0, 7.8; *n* = 10) at month 36. During follow-up, 8 participants (33.3%) decreased or discontinued opioid use throughout follow-up and 4 (16.7%) reported fractures. Median (min, max) EQ-5D-3L utility scores improved from 0.21 (– 0.26, 0.60; *n* = 24) at baseline by 0.15 (– 0.36, 0.91; *n* = 24) at month 6 and were similar throughout follow-up. Injection site reactions were the most common treatment-related EOI, reported in 17 participants (60.7%). Three participants reported treatment-related serious adverse events.
***Conclusion*:** Asfotase alfa treatment improved mobility, physical function, pain, and HRQoL and was well tolerated. These data show the benefit of asfotase alfa in adults with paediatric-onset HPP.

PLAIN LANGUAGE SUMMARY

Hypophosphatasia is a rare disease that can cause broken bones, difficulty walking, and pain. Asfotase alfa is a drug that helps correct the underlying cause of hypophosphatasia. The goal of this study was to see if asfotase alfa helps adults in the UK who have had signs and symptoms of hypophosphatasia since childhood to improve their mobility, pain levels, and quality of life. The study also measured any harms that could come from taking asfotase alfa. Participants took asfotase alfa for at least 6 months and for up to 5 years. The average age of the 24 participants in the study was 42.5 years at the start of treatment. Treatment with asfotase alfa led to improvements in the participants' walking ability and mobility, with effects first observed 6–12 months after starting treatment. Treatment with asfotase alfa also decreased participants' pain ratings and improved their quality of life after 6–12 months of treatment. Improvements in each of these measures were maintained throughout 5 years of treatment. Over half of the participants reported skin reactions at the site where asfotase alfa was injected; this was the most common side effect in all participants. The results from this study show that asfotase alfa treatment can help improve the signs and symptoms of hypophosphatasia in adults and that the treatment is generally safe.

Keywords: 6-Minute Walk Test; Asfotase alfa; Hypophosphatasia; Quality of life; Rare disease

Key Summary Points
Why carry out this study?
Hypophosphatasia (HPP) is a rare, inherited disease characterised by skeletal and non-skeletal manifestations, including increased risk of fractures, poor mobility, and chronic pain.
This analysis was performed to evaluate the efficacy and safety of the enzyme replacement therapy asfotase alfa in adults with HPP who live in the UK.
What was learned from the study?
Treatment with asfotase alfa improved mobility, pain, and quality of life in adults with HPP.
This data collection contributes to a growing body of research demonstrating the efficacy of asfotase alfa for treatment of HPP.
The results of this analysis warrant further investigation of asfotase alfa for the treatment of HPP in diverse geographical settings.

INTRODUCTION

Hypophosphatasia (HPP) is a rare inherited disease that primarily affects bone and dental tissue, but also affects non-skeletal tissues. HPP is caused by either homozygous/compound heterozygous (biallelic) or heterozygous (monoallelic) *ALPL* gene variants resulting in deficient activity of the tissue–non-specific alkaline phosphatase (ALP) enzyme [1–4]. Biochemically, low tissue–non-specific ALP activity results in extracellular accumulation of inorganic pyrophosphate, pyridoxal 5′-phosphate, and phosphoethanolamine [1, 2, 5, 6]. Inorganic pyrophosphate inhibits bone mineralisation, implicating its accumulation in skeletal outcomes [2, 6]. Pyridoxal 5′-phosphate is the circulating form of vitamin B_6, and its inadequate dephosphorylation in HPP may result in vitamin B_6-responsive seizures in infants [6].

Patients with HPP can experience a broad range of clinical manifestations which typically involve impaired bone mineralisation, which can include osteomalacia, skeletal deformities, fractures or pseudofractures (often of the femoral shaft or metatarsals), or premature loss of deciduous teeth [1–3, 7, 8]. However, non-skeletal signs and symptoms, such as pain and muscle weakness, fatigue, chondrocalcinosis, ectopic ossification/calcification of ligaments, calcium pyrophosphate deposition disease (pseudogout), and nephrocalcinosis, are other clinical manifestations reported among patients with HPP [2, 9, 10]. The cumulative burden of disease associated with HPP is high, with patients experiencing fractures, chronic pain, limited mobility, and decreased health-related quality of life (HRQoL) [10–12]. Further, because of the heterogeneous nature of HPP and the variation in clinical manifestations in patients at different ages, misdiagnosis is common and diagnosis can often be delayed [2, 13].

Asfotase alfa (Strensiq®; Alexion, AstraZeneca Rare Disease, Boston, MA, USA) is a human recombinant tissue–non-specific ALP enzyme replacement therapy for the treatment of patients with HPP. Clinical studies have shown that asfotase alfa treatment reduced circulating inorganic pyrophosphate and pyridoxal 5′-phosphate concentrations in adolescents and adults who first manifested symptoms of HPP before age 18 years [14, 15]. Asfotase alfa treatment improved physical functioning and quality of life in several real-world analyses, longitudinal analyses, and randomised controlled trials, while being generally well tolerated [3, 14, 16–18].

Asfotase alfa received marketing approval in the United States and Europe in 2015. In the United Kingdom, the National Institute for Health and Care Excellence (NICE) issued an interim funding recommendation based on a Managed Access Agreement (MAA) which defined the conditions under which patients can receive asfotase alfa. The MAA also required collection of safety and effectiveness data from enrolled participants for a period of 5 years. Conversely, in Japan, asfotase alfa was approved for treatment of patients regardless of age at first symptom manifestation. In most other countries and regions, asfotase alfa was approved in patients with perinatal/infantile- and juvenile-onset HPP [7]. The objective of the current analysis was to assess the safety and effectiveness of asfotase alfa in adults enrolled in the UK MAA to determine whether adult patients will benefit from treatment in routine clinical practice. The data collected during the MAA were submitted to NICE for final evaluation of asfotase alfa.

METHODS

Study Design and Ethical Approval

This analysis used prospective data collected from participants enrolled in the MAA for asfotase alfa treatment between November 20, 2017, and February 2, 2023. The project complied with all relevant data protection and privacy regulations, including the European Data Protection Act and/or institution-/country-specific participant privacy requirements and was performed in accordance with the Declaration of Helsinki. All participants were informed of the use and disclosure of their data, and all consented to participate in the MAA, including attending regular appointments and completing

questionnaires, and to have their data entered into the MAA database.

Eligibility Criteria

To enrol in the MAA, participants must have met certain entry criteria. Participants must have been ≥ 18 years of age at the time of treatment initiation and have received a diagnosis of paediatric-onset HPP, regardless of current age. In the UK, diagnosis of HPP is made on the basis of radiographic and physical manifestations and detection of low serum alkaline phosphatase activity. The diagnosis must have been confirmed by one of seven national HPP expert centres for adult participants and made according to national guidelines for enrolment. Participants were also required to have at least two of the following inclusion criteria: (1) current fractures with a history of non-traumatic or recurrent, non-healing, or poorly healing fractures; (2) continuing or recurring musculoskeletal pain that affects quality of life and is not improved by two types of analgesics; and (3) limited mobility as assessed by a specialist (Bleck score between 1 and 6; Supplementary Material Table S1). Participants were excluded if asfotase alfa was contraindicated for any reason, if they were diagnosed with a terminal disease (e.g., cancer, catastrophic brain injury) which would prevent assessment of the long-term benefit of asfotase alfa, or if they or their legally authorised representative refused to sign the informed consent or were unwilling to comply with the monitoring criteria required for the study.

Withdrawal Criteria

Criteria for non-response were predetermined. Participant cases were referred to the HPP expert committee for confirmation of asfotase alfa discontinuation if one or more of the following three criteria were met: (1) continued fractures over 3 years; (2) failure to achieve substantial reduction in frequency of dose of analgesics or failure to achieve improvement in pain and HRQoL as measured by the Brief Pain Inventory Short Form (BPI-SF; improvement of less than two points) and utility derived from the 5-level EQ-5D version (EQ-5D-5L; defined as failure to improve by at least 0.15); and (3) no improvement or improvement less than the minimum clinically important difference (MCID) in physical function as measured by 6-Minute Walk Test (6MWT) or a decrease of > 1 in the Bleck scoring test. The MCID for the 6MWT was defined as 25 m or 10% relative to baseline.

Outcome Measures and Assessments

Outcome measures assessed throughout data collection in the MAA are described in Table 1 [19–22]. Serious adverse events and events of interest during follow-up were recorded. Events of interest included lack of efficacy, respiratory depression, pneumonia, conductive deafness, craniosynostosis, ectopic calcification, injection-associated reaction, injection site reaction, severe hypersensitivity reaction, systemic immune complex-mediated reactions, neurological event, medication error, off-label use, suspected transmission of infectious agent, pregnancy, breastfeeding, occupational exposure, and/or product abuse/overdose/misuse. Injection site reactions were defined as events localised to the site of asfotase alfa administration that occurred at any time after asfotase alfa administration during MAA participation, and were assessed by investigator judgement as possibly, probably, or definitely related to asfotase alfa.

Statistics and Analysis

The safety population was defined as enrolled participants who received at least one dose of asfotase alfa. The effectiveness analysis population was defined as all participants with a minimum exposure to asfotase alfa of at least 6 months. The number of participants assessed at each timepoint varied because enrolment in the MAA was completed on a rolling basis at different timepoints within the analysis period and because the MAA was observational and all assessments occurred under routine clinical care. Descriptive statistics for 6MWT, Bleck score, BPI-SF, and EQ-5D-5L are reported at baseline and at months 3, 6, 12, 24, and 36.

Table 1 Summary of outcome measures and assessments

Outcome	Metric	Description of measurement
Mobility	6MWT [19]	Distance walked in metres over 6 min and percentage of predicted distance walked
Walking ability	Bleck scale [20]	Assesses walking ability on a scale from 1 (non-walker older than 2 years of age) to 9 (community walker without the use of crutches or canes)
Pain	BPI-SF [21]	Provides a pain severity from an average of four categories, including worst pain, least pain, average pain, and pain right now on a scale from 0 (no pain) to 10 (pain as bad as you can imagine)
Fractures	Occurrence of new and ongoing fractures after treatment initiation, including time to new fractures and the number and location of new fractures	
Analgesic use	History of pain treatment, number of participants treated with pain medication as of last follow-up visit, current number of and change in pain medications, number of pain medications ever used, and class of pain medication (opioid vs. non-opioid)	
Quality of life	EQ-5D-5L[a] HRQoL questionnaire [22]	5 items assessing dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, each measured on a 5-point scale from 1 (indicating no problem) to 5 (indicating extreme problems). Scores can be converted to a health state with a single index value ranging from 1 (full health) to 0 (death). The EQ-5D-3L utility score was mapped from the results of the EQ-5D-5L questionnaire

6MWT 6-Minute Walk Test, *BPI-SF* Brief Pain Inventory Short Form, *HRQoL* health-related quality of life

[a]Permission was acquired from the EuroQol Research Foundation to use the EQ-5D-5L paper version

While the MAA program extended through 5 years, data for these outcomes are reported through month 36 because of low enrolment in the MAA from months 36 through 60, which limits conclusions that can be drawn from the data. For each of these outcomes, 95% confidence intervals (CIs) were calculated for each timepoint relative to baseline. Analgesic use, fracture incidence, and adverse events were recorded continuously and are reported throughout last follow-up. Serious adverse events of interest and deaths are summarised for all participants.

RESULTS

Participants

Overall, 28 adults were enrolled in the MAA between November 20, 2017, and February 2,

2023, and were treated with asfotase alfa. All 28 treated participants were included in the safety analysis population, while 24 were included in the effectiveness analysis population. All participants in the effectiveness analysis population were naive to asfotase alfa at time of enrolment. Four participants had not completed 6 months of asfotase alfa treatment at the cutoff date and, therefore, were not included in the effectiveness analysis population. One additional enrollee died before initiating treatment with asfotase alfa and was not included in the safety or effectiveness analysis populations. No participants discontinued treatment for meeting withdrawal criteria.

Participant demographics are summarised in Table 2. Adult participants enrolled and started treatment in the MAA at a median age of 42.5 years and had experienced HPP-related symptoms since a median age of 5 years. Of 15 participants with available *ALPL* variant data, 12 were compound heterozygotes and 3 were heterozygotes; all initiated treatment at the time of MAA enrolment. Most participants (87.5%) initiated treatment with asfotase alfa at a dose of 6 mg/kg per week administered as either 1 mg/kg 6 times per week (8 participants) or 2 mg/kg 3 times per week (13 participants) (Table 3). Most participants (70.8%) remained stable on the starting dose through latest follow-up, with 1 participant (4.2%) receiving an increased dose (from 1 mg/kg 3 times per week to the licensed dose of 1 mg/kg 6 times per week) and 6 (25.0%) receiving a decreased dose. Reasons for dose decreases included lipohypertrophy, lipodystrophy, fatigue, local injection reaction, extensive skin necrosis, and hip fracture unrelated to treatment. At latest follow-up, participants had been taking asfotase alfa for a median 2.4 years. One participant discontinued treatment because of severe changes at the injection site.

Mobility Assessments: 6MWT and Bleck Score

Participants showed improved or stable walking ability on the 6MWT during follow-up. The median (min, max) distance walked on the 6MWT at baseline was 172.5 m (0.0, 380.0; n = 24) (Fig. 1A). Median (min, max) distance walked increased significantly to 294 m (0, 660;

Table 2 Participant demographics and baseline characteristics

	Effectiveness analysis population (n = 24)
Age at enrolment, median (min, max), years	42.5 (22.0, 61.0)
Age at HPP symptom onset, median (min, max), years	5.5 (0, 15.0)
Age at diagnosis of HPP, median (min, max), years	27.0 (0, 59.3)
Age at treatment initiation, median (min, max), years	42.6 (22.3, 61.1)
Sex, n (%)	
Male	7 (29.2)
Female	17 (70.8)
Distance walked in 6MWT at baseline, median (min, max), metres	172.5 (0.0, 380.0)
Bleck score at baseline, median (min, max)	6.0 (2.0, 9.0)
BPI-SF score at baseline, median (min, max)	8.0 (4.3, 10.0)
EQ-5D-3L score at baseline, median (min, max)	0.21 (− 0.3, 0.6)

6MWT 6-Minute Walk Test, *BPI-SF* Brief Pain Inventory Short Form, *HPP* hypophosphatasia

Table 3 Asfotase alfa treatment characteristics

	Effectiveness analysis population (*n* = 24)
Asfotase alfa dosing at treatment initiation, *n* (%)	
< 6 mg/kg per week	3 (12.5)
6 mg/kg per week	21 (87.5)
1 mg/kg 6 times per week	8 (38.1)
2 mg/kg 3 times per week	13 (61.9)
> 6 mg/kg	0
Change in weekly dose from treatment initiation to last follow-up, *n* (%)	
Dose decrease	6 (25.0)
Dose stable	17 (70.8)
Dose increase	1 (4.2)
Duration of asfotase alfa treatment, median (min, max), years	2.4 (0.7, 4.6)

n = 16) at month 6 and was sustained at month 36 (300 m [150, 600; *n* = 9]). Increases in distance walked exceeded the prespecified MCID of 25 m in 13 participants (76%) at month 6 and in 9 participants (100%) at month 36. The 6MWT median (min, max) percent of predicted walked was 30.4% (5.6%, 59.3%; *n* = 22) at baseline and increased by a median (min, max) 30.7% (– 28.7%, 81.6%; *n* = 15) at month 6; the increase was sustained through month 36 (*n* = 9) (Fig. 1B). This increase was greater than the prespecified MCID of 10%. No participant had a decrease in Bleck score from baseline. Median (min, max) Bleck score increased over time, from 6.0 (2.0, 9.0; *n* = 24) at baseline to 6.5 (5.0, 9.0; *n* = 10) at month 36, for a median (min, max) increase of 2.0 (0.0, 7.0) (Fig. 2).

Pain Assessments

Participants demonstrated a median (min, max) change in aggregate BPI-SF pain score of – 3.3 (– 8.6, 0.0), improving from a median (min, max) of 8.0 (4.3, 10.0; *n* = 24) at baseline to 4.4 (1.0, 7.8; *n* = 10) at month 36, indicating overall clinical benefit (Fig. 3). Median BPI-SF scores significantly decreased after 3 months of treatment with asfotase alfa and continued to decrease through month 36. Use of pain medications at baseline and during treatment with asfotase alfa is summarised in Table 4. At enrolment, 15/24 participants (62.5%) were taking some form of analgesic, but by the last follow-up, all participants (*n* = 24) were taking pain medication. However, eight participants were able to discontinue at least one opioid medication that they had been taking at baseline, and four of these participants were able to discontinue all opioid pain medications. Dose adjustments in non-opioid analgesics are summarised in Supplementary Material Table S2.

Fractures

A total of six fractures occurred in four participants after enrolment in the MAA (Table 5). One fracture occurred between enrolment and the first dose of asfotase alfa, and another occurred 7 days after treatment initiation. These fractures, as well as a metatarsal fracture that occurred in one of these participants 3 years later, resolved with conservative management. The remaining

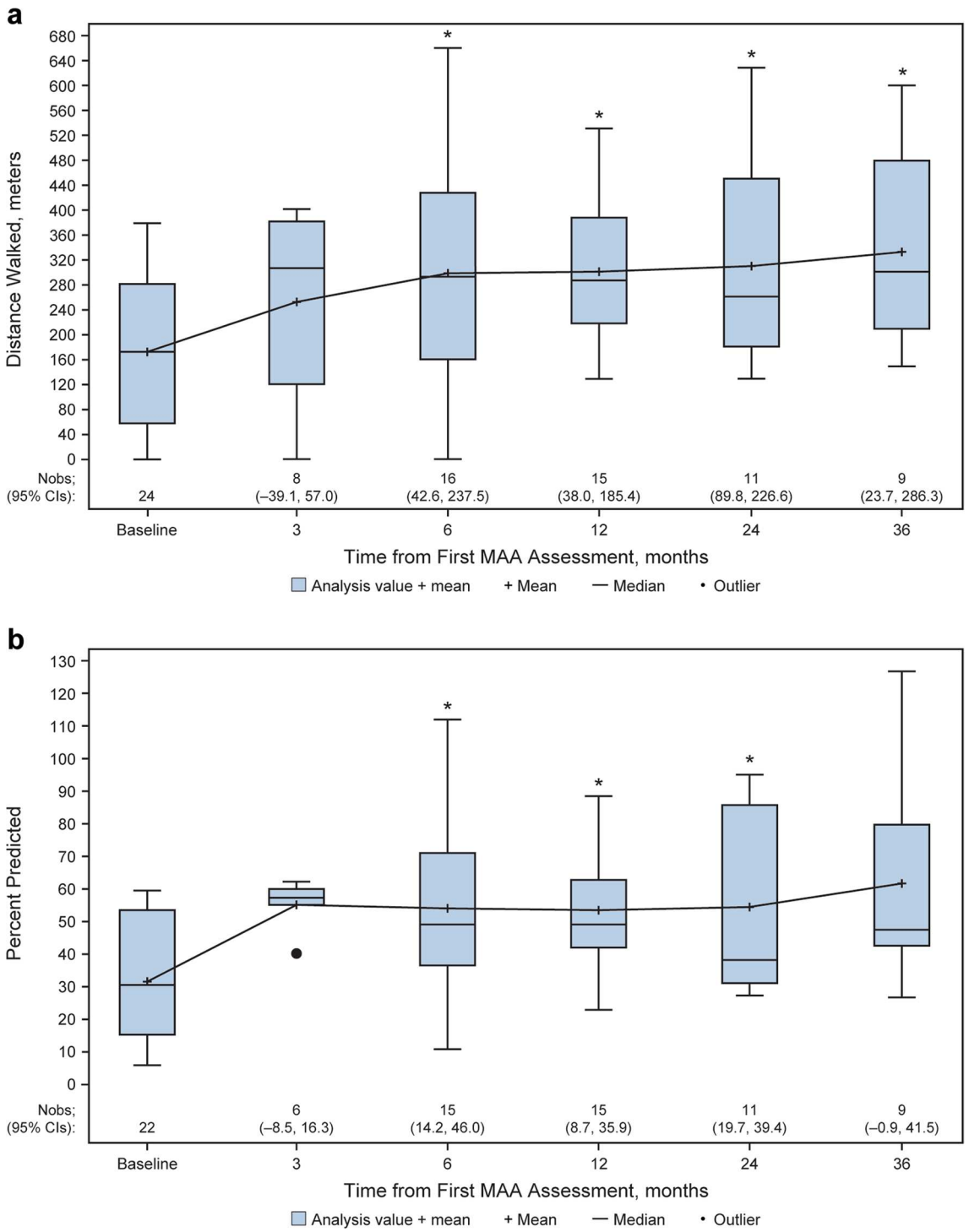

Fig. 1 Change in 6MWT results over time: (**a**) distance walked and (**b**) percent predicted distance walked. *6MWT* 6-Minute Walk Test, *CI* confidence interval, *MAA* Managed Access Agreement, *Nobs* number of observations/participants. *Significant based on 95% CIs

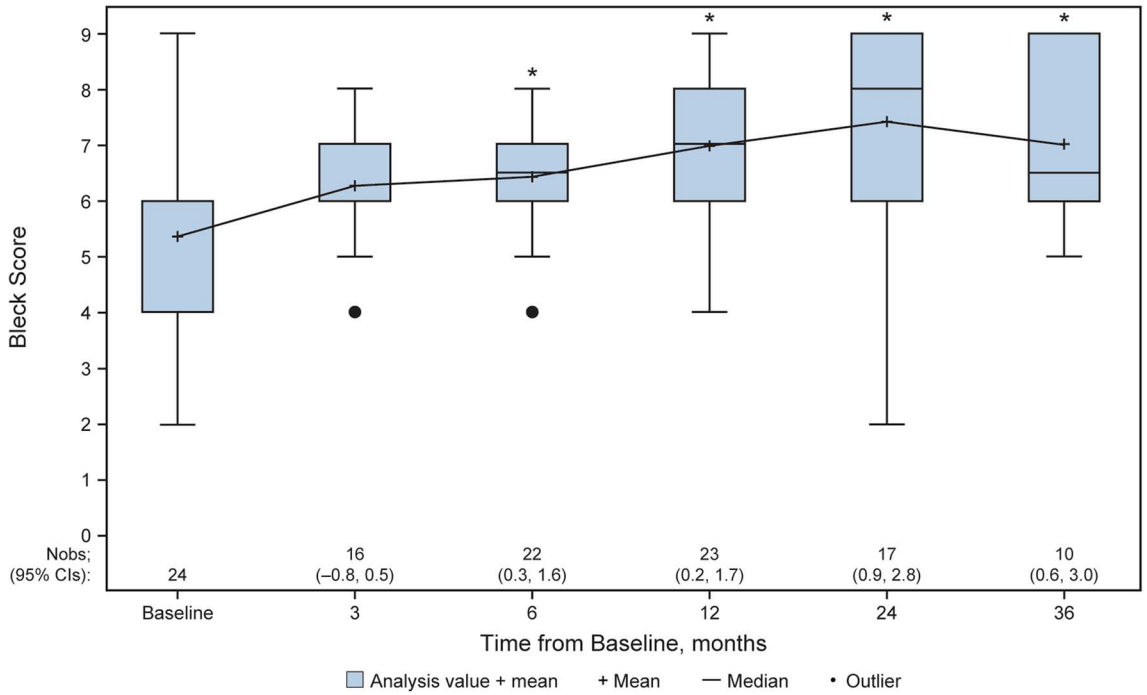

Fig. 2 Change in Bleck score over time. *CI* confidence interval, *Nobs* number of observations. *Significant based on 95% CIs

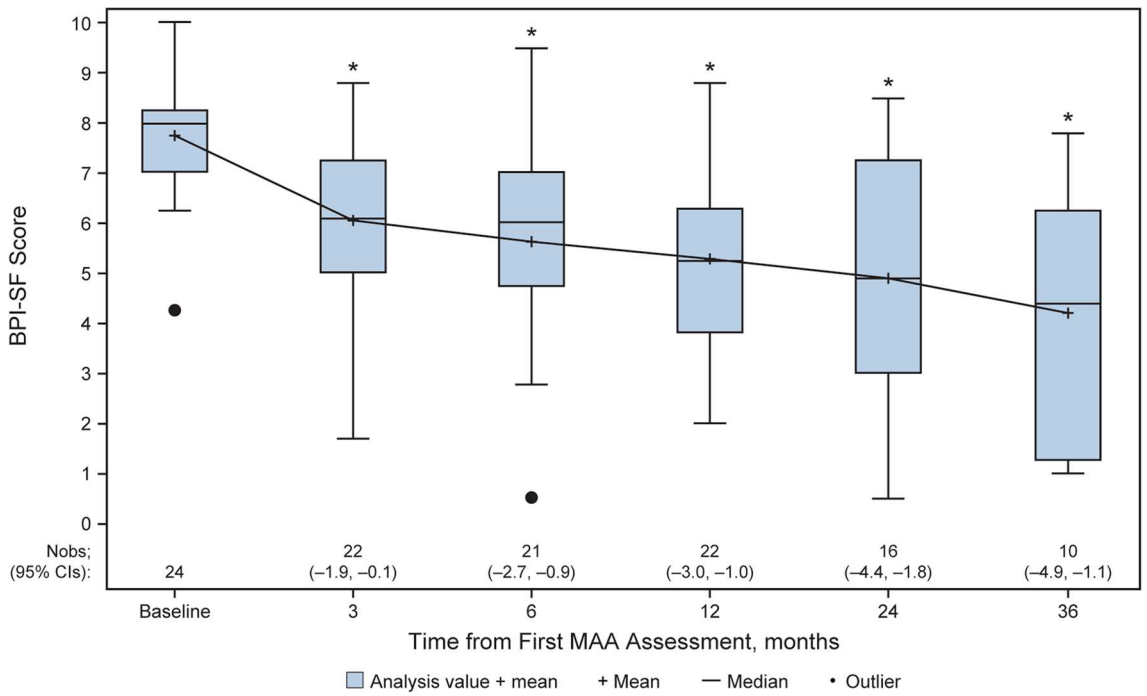

Fig. 3 Change in BPI-SF over time. *BPI-SF* Brief Pain Inventory Short Form, *CI* confidence interval, *MAA* Managed Access Agreement, *Nobs* number of observations/participants. *Significant based on 95% CIs

Table 4 Use of pain medications

	Effectiveness analysis population (*n* = 24)
Participants with no record of pain medications, *n* (%)	0 (0)
Ever on pain medications during MAA, *n* (%)	24 (100)
On pain medications at enrollment, *n* (%)	15 (62.5)
Number of pain medications used per participant among those using pain medications at enrollment, median (min, max)	2 (1, 5)[a]
Started pain medications after enrolment, *n* (%)	9 (37.5)
Using pain medications at last follow-up, *n* (%)	24 (100)
Number of pain medications used per participant among those using pain medications at last follow-up, median (min, max)	3 (1, 5)
Class of pain medications used among participants using pain medications at last follow-up, *n* (%)	
Opioid	20 (83.3)
Non-opioid	24 (100)
Duration of pain treatment among those currently using pain medications at last follow-up, median (min, max), years	3.7 (0.7, 29.0)[b]
Stopped all pain medications, regardless of start date, *n* (%)	1 (4.2)
Discontinued at least 1 opioid medication	8 (33.3)
Discontinued all opioid medication	4 (16.7)

MAA Managed Access Agreement
[a]*n* = 7; [b]*n* = 20

three fractures occurred in two participants (hip fracture in one participant and two independent metatarsal fractures in one participant) more than 12 months after treatment initiation. The hip fracture was treated with a dynamic hip screw and the metatarsal fractures were treated conservatively; fracture healing was not confirmed as resolved at the end of the MAA.

HRQoL

Overall, participants in the analysis population demonstrated EQ-5D-3L utility scores that indicated improved HRQoL (Fig. 4). Median (min, max) EQ-5D-3L utility score was 0.21 (– 0.26, 0.6; *n* = 24) at baseline and significantly increased by 0.31 (– 0.26, 0.70; *n* = 23) and 0.39 (– 0.34, 0.73; *n* = 10) at months 12 and 36, respectively. Overall, 8/10 participants had greater than 0.15-point increases in EQ-5D-3L utility score at month 36.

Adverse Events

Non-serious and serious adverse events of interest and all serious adverse events were recorded and are summarised in Table 6. The most common events of interest regarded as related to treatment with asfotase alfa were injection site reactions [34 injection site reactions in 17/28 participants (60.7%)] and injection-associated reactions [five injection-associated reactions in

Table 5 Fractures after enrolment

Participant number	Total number of fractures	Fracture location(s)	Timing of fracture(s)	Resolution status at end of MAA
1	2	Left femoral neck	Before treatment initiation	Resolved with conservative management
		Metatarsals	> 12 months after treatment initiation	Treated with a boot and resolved
2	1	Vertebral column	< 6 months after treatment initiation	Resolved with conservative management
3	2	2nd metatarsal	> 12 months after treatment initiation	Not confirmed as resolved
		3rd metatarsal	> 12 months after treatment initiation	Not confirmed as resolved
4	1	Hip	> 12 months after treatment initiation	Not confirmed as resolved

MAA Managed Access Agreement

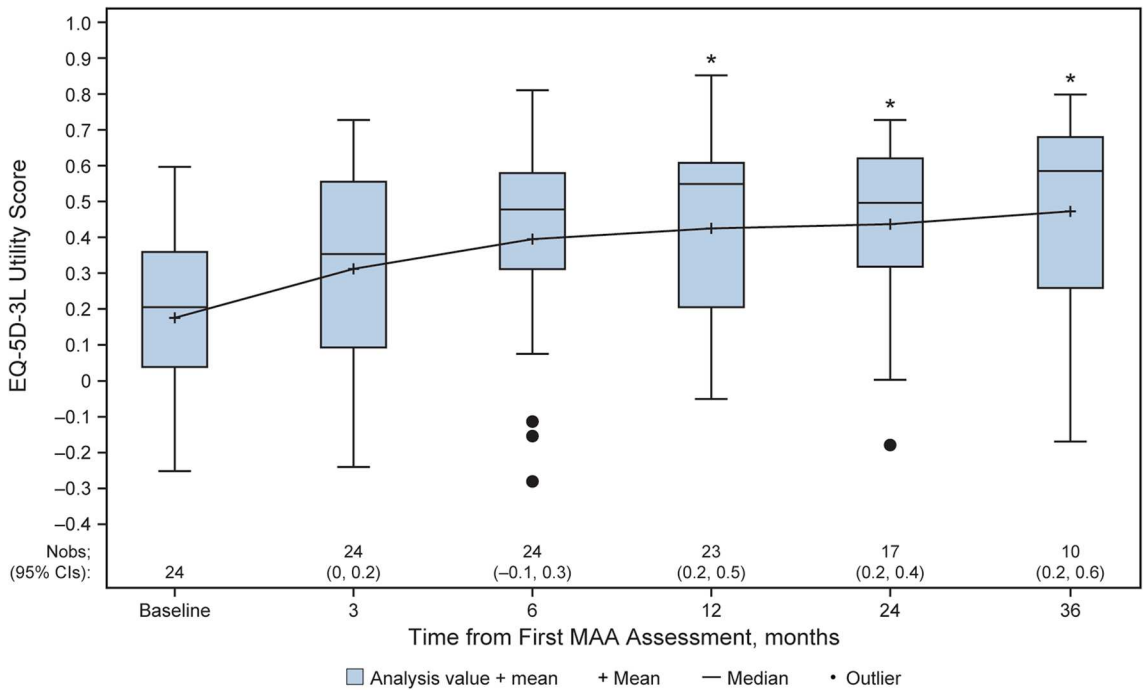

Fig. 4 Total EQ-5D-3L utility scores over time. *CI* confidence interval, *MAA* Managed Access Agreement, *Nobs* number of observations/participants. *Significant based on 95% CIs

5/28 participants (17.9%)]. All but one of the events of interest [42/43 (97.7%)] were mild or moderate in intensity, and 40/43 (93.0%) of the events of interest were considered related to treatment. A total of seven serious adverse events occurred in six participants (21.4%). Three of these events (arthralgia, injection site reaction, and oropharyngeal dysesthesia) were considered related to asfotase alfa treatment.

Table 6 Adverse events of interest and serious adverse events during follow-up

n (%)/*n* of events	Safety population (n = 28)		
	Any	Treatment related[a]	Not related[a]
Events of interest	21 (75.0)/43	20 (71.4)/40	2 (7.1)/3
Injection site reaction	18 (64.3)/35	17 (60.7)/34	1 (3.6)/1
Injection-associated reaction	6 (21.4)/7	5 (17.9)/5	1 (3.6)/2
Medication error	1 (3.6)/1	1 (3.6)/1	0
Serious adverse events			
Arthralgia	1 (3.6)/1	1 (3.6)/1	0
Flank pain	1 (3.6)/1	0	1 (3.6)/1
Injection site reaction	1 (3.6)/1	1 (3.6)/1	0
Hip fracture	1 (3.6)/1	0	1 (3.6)/1
Breast cancer	1 (3.6)/1	0	1 (3.6)/1
Oropharyngeal dysesthesia	1 (3.6)/1	1 (3.6)/1	0
Bone operation	1 (3.6)/1	0	1 (3.6)/1

[a]Categories are not mutually exclusive

DISCUSSION

The results of this analysis of data from adults enrolled in the MAA demonstrate that asfotase alfa improved walking ability, physical functioning, and HRQoL, and reduced pain, confirming the results of earlier studies [3, 14, 16–18]. No participant met the criteria for stopping therapy because of clinical deterioration as measured by decreases in 6MWT or Bleck score greater than the MCID, increases in pain severity as measured by BPI-SF score, or worsening in HRQoL as measured by EQ-5D-3L utility score.

Patients in this analysis first displayed signs and symptoms of HPP at a median age of 5.5 years, with all experiencing signs and symptoms by age 15. Despite this, the median age of diagnosis was 27.0 years (range: 0–59.3 years). These findings are in agreement with previous reports showing median diagnostic delays of 13–25 years among adults with HPP and highlight chronic misdiagnosis as an outstanding problem in treatment of patients with HPP [13, 23].

The median increase in distance walked in the 6MWT was 157.3 m by 6 months of treatment, reaching a median distance of 294.0 m, and an increase was sustained through 36 months (169 m); these improvements were substantially greater than the prespecified MCID of 25 m. Similarly, the median percent predicted 6MWT distance walked increased by 30.7% by month 6, and improvement was sustained at more than the prespecified 10% MCID through 36 months. The median improvement in the Bleck score was two points from baseline to month 36, again reaching the prespecified MCID. The median Bleck score increased from 6.0 at baseline to 6.5 at month 36. Bleck scores of 6 and 7 correspond with the ability to walk up to 300 m (2–3 blocks) with use of crutches or canes and the ability to walk up to 300 m without any aids, respectively [24]. Taken together, these results demonstrate that the improvement in mobility and physical functioning are realised early and sustained through at least 3 years, validating and expanding on results of earlier studies [25].

All 24 participants had pain medications reported, including 20 participants with opioid

use, before or after asfotase alfa initiation. More participants were taking at least one analgesic at the end of the study compared with time of enrolment. However, four participants were able to reduce the number of opioid medications they were taking during treatment with asfotase alfa, and another four participants were able to discontinue all opioids. The increased number of patients taking analgesics at the end of the study was potentially caused by increased mobility throughout the treatment period, as measured by the 6MWT and Bleck assessment—although increased analgesic use may have also contributed to improved mobility. Other potential reasons for the increase require further assessment.

Pain is one of the principal contributors to poor HRQoL in adults and children with HPP [10, 11, 26]. Overall, there was a substantial improvement in HRQoL measures, as determined using EQ-5D-3L in the current analysis, corresponding with the decrease in opioid analgesic use and decrease in BPI-SF scores. Some participants experienced a range of conditions unrelated to treatment or HPP, including a breast cancer diagnosis, depression, anxiety, and the effects of the COVID-19 pandemic that may have affected some of the responses to the quality-of-life questionnaires.

Asfotase alfa was generally well tolerated, with almost all adverse events being mild or moderate in severity. The most common adverse events related to treatment were injection site reactions and injection-associated reactions. This is consistent with results of prior studies [3, 14, 16–18]. Although three serious adverse events in this analysis were attributed to asfotase alfa, few serious adverse events have been reported in prior studies of asfotase alfa. Two of the five prior published studies reported serious adverse events [3, 14, 16–18]. In one study, of the 29 serious adverse events reported in 9 participants, eight events in 2 participants were assessed as being related to asfotase alfa treatment; one participant withdrew from this study after an anaphylactoid reaction [14].

The UK adult data submitted to the MAA, alongside the results of the prior studies of asfotase alfa, prompted NICE to recommend asfotase alfa as a treatment option for adults with paediatric-onset HPP whose symptoms started before age 6 months [27]. Asfotase alfa is also recommended for adults whose symptoms started between ages 6 months and 17 years if they have two or more of the following: current fractures with a history of non-traumatic, recurring, or non-healing or poorly healing fractures; limited mobility assessed by a specialist using the modified Bleck Ambulation Efficiency Score and a Bleck score between 1 and 6; or clinically significant continuing or recurring musculoskeletal pain which affects daily activities and HRQoL and has not improved after two different classes of analgesic recommended by a national pain specialist.

This analysis has some limitations. It is difficult to assess the fracture data in treated participants in the absence of an untreated comparator arm. However, there were few fractures in this cohort, with only 4/24 participants experiencing a fracture during follow-up. This compares with an overall observed history of fractures in the Global HPP Registry of 62.1% in untreated participants [12]. While BPI-SF pain scores showed improvement over time with asfotase alfa treatment, analgesic use also increased over time, limiting the interpretability of these results. The MAA took place during the COVID-19 pandemic, causing many participants to miss at least one assessment and limiting the amount of data collected. The COVID-19 pandemic-related lockdowns may also have affected the answers of the participants to the daily activities and depression/anxiety components of the EQ-5D-5L questionnaire. The data are also limited by the observational nature of the MAA in which data were collected under routine clinical care and by rolling enrolment of participants into the MAA, both of which result in variable participant numbers throughout follow-up.

CONCLUSIONS

Treatment with asfotase alfa resulted in improved mobility, physical function, pain, and HRQoL, confirming the clinical benefit of asfotase alfa in adults with paediatric-onset HPP. Asfotase alfa was well tolerated, and no new

safety signals were identified during the 5-year data collection period.

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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. Katie E. Moss reports support for advisory board participation/presentations from Alexion, AstraZeneca Rare Disease and receipt of educational grants from AbbVie; Amgen; Alexion, AstraZeneca Rare Disease; Novartis; and UCB. Richard Keen reports support for advisory board participation/presentations from Alexion, AstraZeneca Rare Disease. Alexandros Zygouras and Shona Fang are employees of Alexion, AstraZeneca Rare Disease and may own stock/options with AstraZeneca. Muhammad Javaid reports speaker honoraria and grants from Amgen, Kyowa Kirin, UCB, AbbVie, Besins Healthcare, and Sanofi. Tarekegn Geberhiwot and Peter Selby report no conflicts. Judith S. Bubbear reports support for speaker/consultancy participation from Alexion, AstraZeneca Rare Disease. Kenneth E.S. Poole reports support from the Cambridge NIHR Biomedical Research Centre. Jennifer S. Walsh reports speaker's honoraria from Eli Lilly, drug donation for clinical studies from Eli Lilly, and consulting fees from Mereo BioPharma.

Ethical Approval. This analysis used prospective data collected from participants enrolled in the MAA for asfotase alfa between November 20, 2017, and February 2, 2023. The project complied with all relevant data protection and privacy regulations, including the European Data Protection Act and/or institution/country-specific participant privacy requirements and was performed in accordance with the Declaration of Helsinki. All participants were informed of the use and disclosure of their data. All patients consented to participate in the MAA, including attending regular appointments and completing questionnaires, and to have their data entered into the MAA database.

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