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ORIGINAL RESEARCH

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

Raja Padidela · Nick Bishop · Paul Arundel · Shona Fang · Alexandros Zygouras · M. Zulf Mughal · Nick Shaw · Vrinda Saraff

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ABSTRACT

***Introduction*:** Hypophosphatasia (HPP) is a rare, inherited metabolic bone disease with a high degree of morbidity and mortality in children. Asfotase alfa is an enzyme replacement therapy for HPP reimbursed in the UK since 2017 under a Managed Access Agreement (MAA). This analysis assessed the effectiveness and safety of asfotase alfa in children < 18 years of age.

***Methods*:** The MAA was a prospective, longitudinal data collection in children with paediatric-onset HPP. Effectiveness outcomes were evaluated in children who were treated with asfotase alfa for ≥ 6 months. Data were collected on respiratory support, growth, mobility, motor development, analgesic use, quality of life, and safety at enrolment and throughout the 5-year MAA.

***Results*:** Twenty-four children enrolled in the MAA and 20 were included in the analysis. Twelve children had received asfotase alfa before enrolment through a clinical trial or compassionate use program. From baseline to month 60, the median (minimum, maximum) change in height and weight *Z*-scores were 0.20 (−0.9, 1.2; $n=6$) and −0.5 (−1.9, 1.5; $n=6$), respectively. The median (minimum, maximum) percent of predicted distance walked in the 6-Minute

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R. Padidela (✉) · M. Z. Mughal
Paediatric Endocrinology, Royal Manchester Children's Hospital, Manchester M13 9WL, UK
e-mail: raja.padidela@manchester.ac.uk

R. Padidela
Faculty of Biology Medicine and Health, University of Manchester and Manchester Academic Health Science Centre, Manchester, UK

N. Bishop · P. Arundel
Sheffield Children's Hospital, Sheffield, UK

N. Bishop
Division of Clinical Medicine, School of Medicine and Population Health, University of Sheffield, Sheffield, UK

S. Fang · A. Zygouras
Alexion, AstraZeneca Rare Disease, Boston, MA, USA

N. Shaw · V. Saraff
Birmingham Women's and Children's Hospital, Birmingham, UK

N. Shaw
Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, UK

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Walk Test increased by 3.8% (−8.6, 4.3; $n=5$) at month 3 and was sustained through follow-up. Median (minimum, maximum) child- and parent-reported Pediatric Quality of Life Inventory scores were 59.2 (15.2, 91.3; $n=11$) and 53.4 (16.3, 100.0; $n=18$) at baseline and increased by 21.7 (5.4, 37.0; $n=3$) and 16.3 (9.8, 45.7; $n=4$) at month 60, respectively. Treatment-naïve children had a greater clinical response than treatment-experienced participants, who maintained their status. No deaths occurred in the study. The most common adverse events were injection site reactions, reported in 8/24 participants (33.3%).

***Conclusion*:** This analysis confirmed the clinical benefit of asfotase alfa in children with HPP. Asfotase alfa was well tolerated, with no new safety signals identified.

PLAIN LANGUAGE SUMMARY

Hypophosphatasia is a rare bone disease that can develop in people of all ages, including children. The signs and symptoms of hypophosphatasia can vary depending on the age of the patient. Children with hypophosphatasia may have pain, poor growth, and overall poor quality of life, as well as difficulty walking, moving, or maintaining good posture. Asfotase alfa (Strensiq®) is a drug that helps treat the cause of hypophosphatasia. The Managed Access Agreement was implemented to see if asfotase alfa helps improve the signs and symptoms of hypophosphatasia in children, and to assess the impact of any unwanted effects of treatment. Children who took the drug had improved physical development through up to 5 years of follow-up. They had improvements in height and weight, ability to walk, and other measures of body movement. Children taking the drug also had improved quality of life after starting treatment with asfotase alfa. Children said their quality of life improved after taking the drug for 6 months. Their parents reported that it took 2.5 years for their children's quality of life to improve. One third of children taking asfotase alfa had a skin reaction at the site of injection, which was the most common side effect reported. Overall, asfotase alfa has an established and well-described safety profile and can help improve physical functioning and quality of life in children with hypophosphatasia.

Keywords: Asfotase alfa; Growth; Hypophosphatasia; Mobility; Pain; Quality of life

Key Summary Points
Hypophosphatasia is a rare, inherited disease that causes pain and impairs growth, mobility, and motor function in affected children
The objective of this data collection was to determine the long-term effectiveness of the enzyme-replacement therapy asfotase alfa on growth, functional outcomes, and quality of life in children with hypophosphatasia who live in the UK
Asfotase alfa improved growth, mobility, motor development, and quality of life in children with hypophosphatasia throughout 5 years of treatment, with positive effects of the drug seen within the 1st year for most metrics and sustained throughout treatment
The results of this analysis support that asfotase alfa is an effective treatment for hypophosphatasia in children

INTRODUCTION

Hypophosphatasia (HPP) is a rare, inherited disease caused by deficient activity of tissue non-specific alkaline phosphatase (ALP) [1, 2], resulting in the accumulation of circulating inorganic pyrophosphate (which inhibits bone mineralization), pyridoxal 5′-phosphate (the circulating form of vitamin B_6), and phosphoethanolamine [1–4]. Recent estimates indicate that the annual

diagnosed prevalence of HPP across all ages is approximately 1.4/100,000 [5]. The birth prevalence of perinatal/infantile HPP has been estimated at about 1/300,000 births in some countries [6]. Although perinatal and infantile HPP has a high incidence of morbidity and mortality [7], the heterogeneous nature of the disease and the variation in disease manifestations in childhood and adulthood often cause delays in diagnosis [2, 8].

Asfotase alfa (Strensiq®; Alexion, AstraZeneca Rare Disease, Boston, MA, USA) is a human recombinant tissue-nonspecific ALP enzyme replacement therapy for the treatment of HPP. Clinical studies of asfotase alfa in children with HPP have demonstrated sustained improvements in HPP-related skeletal abnormalities seen on radiographs as well as reductions in circulating levels of both inorganic pyrophosphate and pyridoxal 5′-phosphate to within normal ranges, indicating effective replacement of the deficient ALP [9, 10]. Asfotase alfa was also associated with improvements in survival, physical development, respiratory function, physical functioning, healing of skeletal manifestations, and quality of life in children with HPP while being generally well tolerated [9–13].

Asfotase alfa received marketing authorization in the US and Europe in 2015 for the treatment of paediatric-onset HPP and in Japan for patients of any age of onset of the disease. In England, 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 the drug under National Health Service England (NHSE). This MAA also required that safety and effectiveness data be collected on enrolled patients for a 5-year period. The objective of the current analysis was to describe the effectiveness and safety of asfotase alfa in children enrolled in the MAA in England, Wales, and Northern Ireland.

METHODS

Study Design and Ethical Approval

Data were collected prospectively from all participants enrolled in the MAA. All enrolled participants (or their legally authorized representative) were informed of the purpose of the data collection project and the expected use of any data collected. 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. The project was conducted in accordance with the Declaration of Helsinki. All participants consented to participate in the MAA, including completing questionnaires and attending appointments, and to have their data entered into the MAA database. The program was started in August 2017 and concluded in February 2023.

Eligibility Criteria

To be part of the MAA, participants must have had a diagnosis of paediatric-onset HPP, regardless of age at enrolment, confirmed by one of the national HPP expert centres. Diagnosis was made based on the presence of persistently low ALP, elevated ALP substrates, and clinical signs and symptoms of HPP. Start criteria for entry into the MAA included continuing or recurring musculoskeletal pain that affects daily activities (for children aged 1–18 years) or missing expected developmental gross motor milestones as assessed by BAMF (for children aged 1–4) or limited mobility assessed by a specialist, with a Bleck score between 1 and 6 (for children aged 5–18). All participants up to 1 year of age presenting with HPP who met these start criteria were also eligible. Eligibility criteria for each participant were submitted for approval to the National Authorisation Panel (consisting of clinical experts and representatives of NHSE and NICE), which also reviewed clinical data annually to assess if continued treatment was necessary.

Participants were excluded from the MAA and data collection, and did not start treatment with asfotase alfa if the drug was contraindicated for any reason, if they were diagnosed with an additional progressive life-limiting condition such that asfotase alfa would not provide long-term benefit (e.g., terminal cancer, catastrophic brain injury) or if they or their legally authorized

Table 1 Summary of outcome measures and assessments

Outcome	Metric	Description of measurement
Respiratory support	Proportion of participants requiring different types of respiratory support, including supplemental nasal oxygen, continuous positive airway pressure, bilevel positive airway pressure, or invasive ventilation, at each visit up to 4 years of age	
Growth	Length/height and weight	Percentiles and *Z*-scores
Mobility	6MWT [14]	Distance walked in meters for 6 min by participants 5 to < 18 years of age
Motor development	10-Point upper and lower extremity scales of BAMF instrument	Measures gross motor function; higher scores indicate higher levels of function [18]. BAMF was performed in children 1 to 4 years of age. Children who received their first dose of asfotase alfa at < 1 year of age were assessed once they reached 1 year of age
Walking ability	Modified Bleck scale	Scored on a scale of 1 to 9; higher scores indicate better walking ability [15, 16]. Bleck scores were assessed in participants 5 to < 18 years of age [15, 16]. Participants are rated as being unable to walk at an age of > 2 years to being able to walk the same distance as their age-adjusted peers without the use of crutches or canes, albeit at a slower pace
Analgesic use	History of pain treatment, number of participants treated with pain medication at last follow-up visit, current number of and change in number of pain medications, number of pain medications ever used, and class of pain medication used (opioid vs nonopioid)	
Quality of life	PedsQL total score [17]	Reported on a scale of 0 to 100; higher scores indicate better quality of life [17]. Recorded by child and/or parent for participants 2 to < 18 years of age

6MWT, 6-Minute Walk Test; BAMF, Brief Assessment of Motor Function; PedsQL, Pediatric Quality of Life Inventory

representative was unwilling to comply with the monitoring criteria required for the MAA or refused to sign the informed consent form. Although participants of all ages were eligible to participate in the MAA, the current analysis focuses on children who were <18 years of age at the time of treatment initiation.

Withdrawal criteria

Criteria for treatment nonresponse were predetermined within the MAA. Participants could be referred to the National Authorisation Panel for consideration of asfotase alfa discontinuation if two or more of the following criteria were met: (1) failure to maintain growth (defined as a drop in height of > 5% from centile line after 1 year on a stable dose of asfotase alfa); (2) no improvement or an improvement of less than the minimal clinically important difference (MCID) in physical function as measured using the 6-Minute Walk Test (6MWT) or a decrease in Bleck score of > 1 level in those ≥ 5 years of age (MCID for 6MWT was determined to be < 25 m or < 10% over baseline); (3) no reduction in pain as assessed by a pain specialist; (4) failure to achieve a substantial reduction in frequency or dose of analgesics; or (5) failure to see an MCID improvement in quality of life (5.16 points for parents' reports and 4.83 points for children's reports) as measured by Pediatric Quality of Life Inventory (PedsQL).

Outcome Measures and Assessments

The outcome measures indicative of HPP disease status assessed in the MAA are summarized in Table 1 [14–18]. Serious adverse events and events of interest during follow-up were also recorded. Injection site reactions, defined as events occurring any time after asfotase alfa administration and localized to the administration site that are deemed by the investigator as possibly, probably, or definitely related to asfotase alfa treatment, were recorded throughout the duration of the MAA.

Table 2 Participant demographics

	Analysis population (*N* = 20)
Age at enrolment, median (minimum, maximum), years	4.2 (0, 17.0)
Age group at enrolment, *n* (%)	
< 1 year	6 (30)
1 to < 5 years	6 (30)
5 to < 18 years	8 (40)
Age at HPP symptom onset, median (minimum, maximum), years	0 (0, 14.0)
Age at diagnosis of HPP median (minimum, maximum), years	0.04 (0, 16.3)
Age at treatment initiation, median (minimum, maximum), years	0.04 (0, 17.7)
Sex, *n* (%)	
Male	9 (45)
Female	11 (55)

HPP, hypophosphatasia

Table 3 Asfotase alfa treatment characteristics

	Safety population ($N = 24$)
Asfotase alfa dosing at treatment initiation, *n* (%)	
< 6 mg/kg per week	2 (8.3)
Median (minimum, maximum)	4.4 mg/kg (3.0, 5.7) per week
Mean (SD)	4.4 (1.9) mg/kg per week
6 mg/kg per week	14 (58.3)
1 mg/kg 6 times per week	0
2 mg/kg 3 times per week	14 (100)
> 6 mg/kg	8 (33.3)
Median (minimum, maximum)	9.0 mg/kg (6.3, 15.9) per week
Mean (SD)	9.6 (3.3) mg/kg per week
Asfotase alfa dosing at last follow-up, *n* (%)	
< 6 mg/kg per week	5 (20.8)
6 mg/kg per week	11 (45.8)
1 mg/kg 6 times per week	0
2 mg/kg 3 times per week	11 (100)
> 6 mg/kg per week	8 (33.3)
Change in weekly dose from treatment initiation to last follow-up, *n* (%)	
Dose decrease	8 (33.3)
Dose stable	10 (41.7)
Dose increase	6 (25.0)
Median minimum dose (minimum, maximum)	9.0 mg/kg (6.0, 18.8) per week
Mean minimum dose (SD)	11.1 (4.8) mg/kg per week
Duration of asfotase alfa treatment, median (minimum, maximum), years	4.2 (0.01, 10.7)

SD, standard deviation

Statistics and Analysis

The safety population included all enrolled participants who had 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 ≥ 6 months. Descriptive statistics of data for each of the outcome measures are presented at baseline, 3 months, 6 months, and every 6 months thereafter. Differences in outcomes over time relative to baseline were assessed by calculating 95% confidence intervals (CIs). Serious adverse events, events of interest, and deaths were recorded for all participants.

RESULTS

Participants

Overall, 24 children 0 to < 18 years of age at baseline were enrolled in the MAA between November 20, 2017, and February 2, 2023, the end of the program, with 20 participants having received asfotase alfa for at least 6 months. Twelve of the 20 (60%) participants in the effectiveness analysis population were treatment-experienced, defined as having received asfotase alfa at or before enrolment as part of a clinical trial or compassionate use program, with a median (minimum, maximum) time on treatment of 3.7 years (0.5, 10.1) before enrolment. Those who initiated asfotase alfa at the time of enrolment in the MAA are referred to as treatment naïve. Participant demographics are summarized in Table 2. Children were enrolled and started treatment at a median (minimum, maximum) age of 4.2 (0.0, 17.0) years, with most having experienced HPP symptoms since the age of approximately 1 year. *ALPL* variant data were available for 13 patients, of whom 6 were heterozygotes and 7 were compound heterozygotes (Supplementary Table S1).

Fourteen of 24 (58%) participants in the safety population initiated treatment with asfotase alfa at the recommended dose of 6 mg/kg per week, with 8 (33%) starting at a higher dose (Table 3). Reasons for starting at a higher dose included severe encephalopathy, poor mineralisation, and respiratory deterioration (Supplementary Table S2). Two participants started at a lower dose (one at 1 mg/kg 3 times per week and one at 1.9 mg/kg 3 times per week). Ten (42%) participants in the safety population remained stable on their starting dose through the latest follow-up, with six (25%) receiving an increased dose (Supplementary Table S3) and eight (33%) receiving a decreased dose. The proportion of participants starting at the recommended dose and remaining stable on their dose was similar in the analysis population. At the latest follow-up, participants had been taking asfotase alfa for a median of 5.0 years.

Two participants discontinued treatment in the MAA. One participant withdrew after receiving a single dose of asfotase alfa because they were uncomfortable with needles; this participant was not included in the effectiveness analysis population. The second participant discontinued treatment because of a change of residency to outside the UK. No deaths occurred during data collection.

Respiratory Support

Overall, three participants required any type of respiratory support during follow-up. All three had a prior history of needing respiratory support and received brief invasive ventilation that ended within 3 months of treatment initiation. The duration of invasive ventilation was 8 days, 12 days, and 3 months in the three participants. All three also received continuous positive airway pressure, which ended within 1 month for two participants and within 6 months for one participant. One of the three also received supplemental oxygen, which also ended within 1 month of treatment initiation. No participant required new invasive ventilation.

Growth

Most participants (18/20) demonstrated stable growth during the MAA, with two participants demonstrating > 5% reductions in their height centile at 18 months through the last follow-up. The median (minimum, maximum) height percentile was 0.77% (0, 39.1) at baseline ($n = 20$) and increased to 3.8% (0, 72.8) at month 60 (95% CI: − 20.1, 12.9; $n = 6$). Figure 1a, b shows height and weight *Z*-scores over time. From baseline ($n = 20$) to month 60 ($n = 6$), the median (minimum, maximum) change in height *Z*-score was 0.20 (− 0.9, 1.2; 95% CI: − 0.9, 1.4) and the median (minimum, maximum) change in weight *Z*-score was − 0.5 (− 1.9, 1.5; 95% CI: − 1.9, 0.5). Participants who had not received asfotase alfa before enrolment in the MAA (treatment naïve) had greater improvements in height and weight *Z*-scores after starting asfotase alfa than those who had received asfotase alfa before enrolment (treatment experienced; Fig. 1c, d).

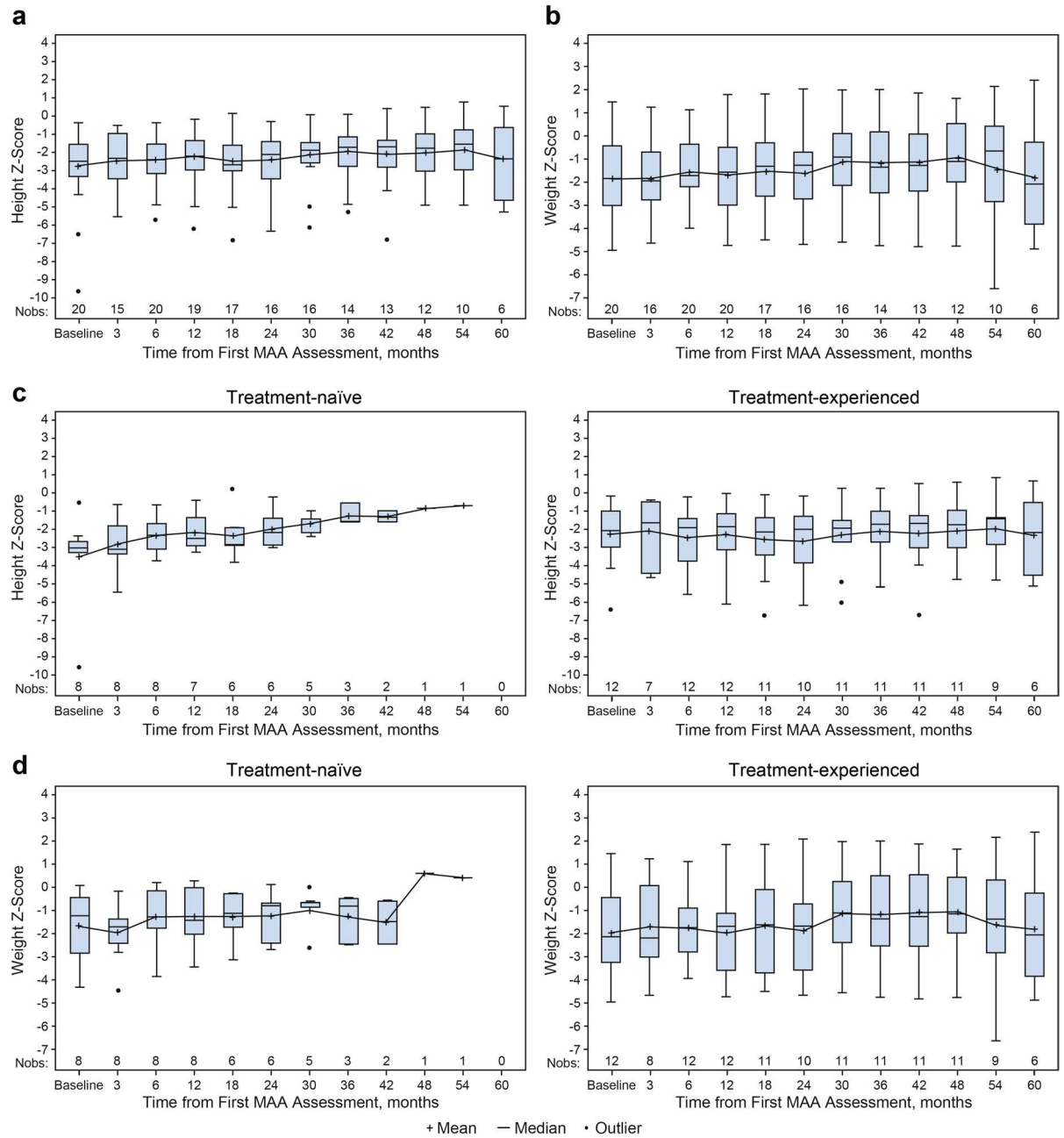

Fig. 1 Box plots showing growth *Z*-scores for **a** height; **b** weight; **c** height, treatment-naïve vs treatment-experienced participants; and **d** weight, treatment-naïve vs treatment-experienced participants. Boxes represent median and interquartile range; whiskers represent minimum and maximum observations. MAA, Managed Access Agreement; Nobs, number of observations

Height *Z*-scores improved by a median (minimum, maximum) of 5.1 (1.6, 8.6; $n=2$) for treatment-naïve participants from baseline to month 42 of treatment compared with 0.2 (−0.9, 1.2; 95% CI −0.9, 1.4) for six treatment-experienced participants from baseline to month 60. Weight

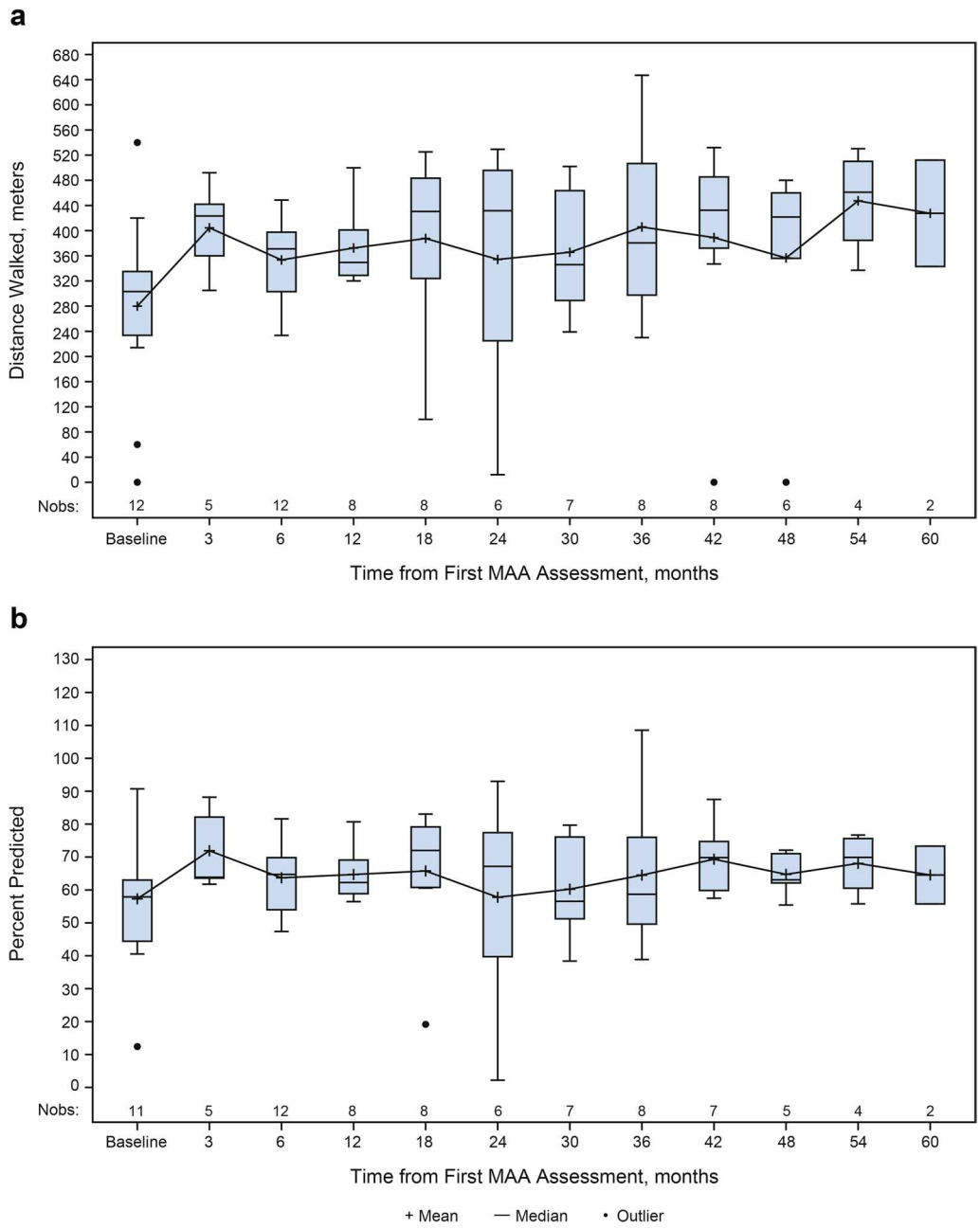

Fig. 2 Box plots showing change in 6MWT over time for children 5 to < 18 years of age: **a** distance walked and **b** percent predicted distance walked. Boxes represent median and interquartile range; whiskers represent minimum and maximum observations. 6MWT, 6-Minute Walk Test; MAA, Managed Access Agreement; Nobs, number of observations

Z-scores improved by a median (minimum, maximum) of 0.9 (−0.1, 1.9; $n=2$) for treatment-naïve participants from baseline to month 42 of treatment compared with a median −0.5 (−1.9, 1.5; 95% CI −1.9, 0.5) change for six treatment-experienced participants from baseline to month 60.

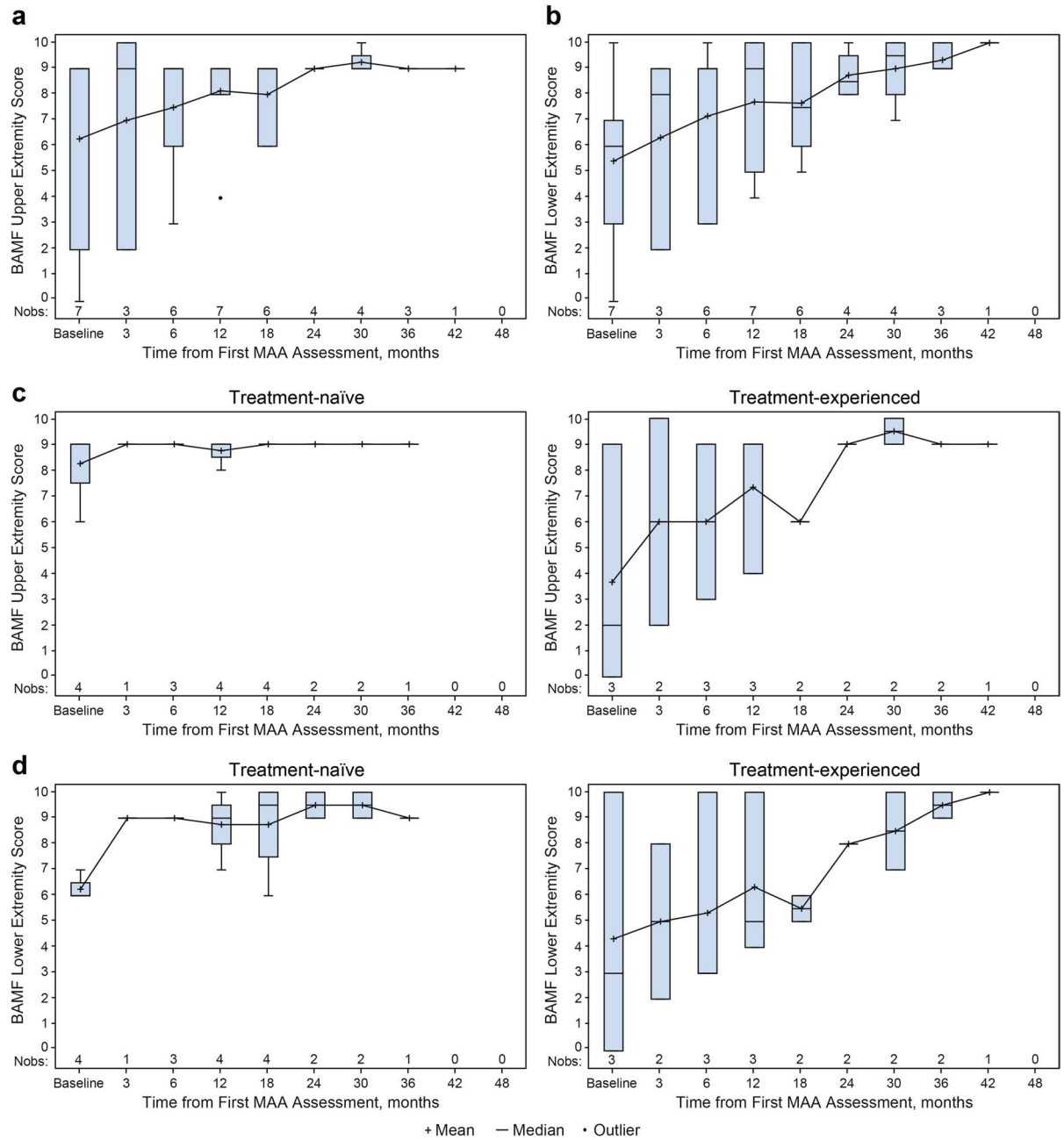

Fig. 3 Box plots showing change in BAMF scores over time: **a** upper extremity; **b** lower extremity; **c** upper extremity, treatment-naïve vs treatment-experienced participants and **d** lower extremity, treatment-naïve vs treatment-experienced participants. Boxes represent median and interquartile range; whiskers represent minimum and maximum observations. BAMF, Brief Assessment of Motor Function; MAA, Managed Access Agreement; Nobs, number of observations

Mobility (6MWT)

Participants 5 to < 18 years of age who were assessed with 6MWT showed stable walking ability during follow-up. The median (minimum, maximum) distance covered on the 6MWT at baseline was 303.1 m (0, 540.0; $n = 12$). The median (minimum, maximum) 6MWT distance walked increased by 27.0 m (– 48.0, 423.3; $n = 5$) at month 3 and was sustained throughout follow-up (Fig. 2a). Improvements represented an increase greater than the prespecified MCID of 25 m at most timepoints from month 3 to month 54 (Fig. 2a). The 6MWT median (minimum, maximum) percent predicted distance walked at baseline was 57.9% (12.4, 90.7; $n = 11$); positive and sustained improvements were observed at most timepoints from month 3 onward (Fig. 2b).

Motor Development (BAMF)

BAMF estimates were determined in 12 participants 1–4 years of age, with 11/12 (91.7%) initiating treatment before reaching 1 year of age. Upper and lower extremity BAMF scores generally increased over time, indicating improvement in mobility and gross motor skills (Fig. 3a, b). Median (minimum, maximum) upper extremity BAMF scores were 9.0 (0, 9.0; $n = 7$) and 9.0 (9.0, 9.0; $n = 3$) at baseline and month 36, respectively, with a median (minimum, maximum) change of 7.0 (3.0, 9.0; 95% CI 3.2, 11.8) during this time. One participant experienced a drop in upper extremity BAMF score from 9 to 6 between month 12 and 18, but the score returned to 9 by month 24. Median (minimum, maximum) lower extremity BAMF scores were 6.0 (0, 10.0; $n = 7$) and 9.0 (9.0, 10.0; $n = 3$) at baseline and month 36, respectively, with a median (minimum, maximum) change of 7.0 (3.0, 7.0; 95% CI 3.2, 11.8) during this time. Among treatment-naive patients, the median change in BAMF score from baseline to month 30 was 1.5 for upper extremities and 3.5 for lower extremities. Among treatment-experienced patients, the median change in BAMF from baseline to month 36 was 8.0 for both the upper and lower extremities. These data indicate an overall trend toward increased upper and lower extremity BAMF scores in both treatment-naïve and treatment-experienced participants, but the number of participants in each of the two groups was very small, especially at the later timepoints (Fig. 3c, d).

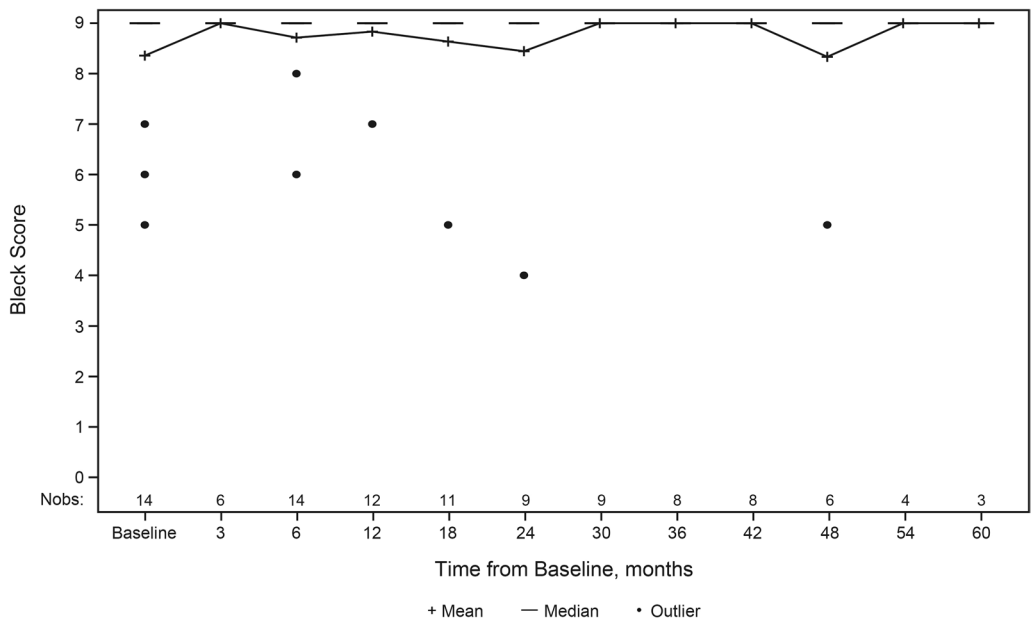

Fig. 4 Change in Bleck scores over time in children aged 5 to < 18 years. Nobs, number of observations

Table 4 Use of analgesics

	Analysis population ($N = 20$)
Patients with no record of pain medications, *n* (%)	7 (35.0)
Ever on pain medications during MAA, *n* (%)	13 (65.0)
On pain medications at enrolment, *n* (%)	4/13 (30.8)
Number of pain medications used per patient among those using pain medications at enrolment, median (minimum, maximum)	2 (1, 2)[a]
Started pain medications after enrolment, *n* (%)	9/13 (69.2)
Stopped all pain medications at last follow-up, *n* (%)	7/13 (53.8)
Using pain medications at last follow-up, *n* (%)	6/13 (46.2)
Number of pain medications used per patient among those using pain medications at last follow-up, median (minimum, maximum)	1 (1, 3)[b]
Duration of analgesic use at last follow-up, median (minimum, maximum), years	0.95 (0.04, 4.62)[c]

MAA, Managed Access Agreement

[a] $n = 4$

[b] $n = 6$

[c] $n = 5$

Walking Ability (Bleck Score)

Overall, participants 5 to < 18 years of age remained at or near the optimal Bleck score of 9 throughout follow-up, indicating a high level of walking ability (Fig. 4). The change in median (minimum, maximum) modified Bleck score from baseline ($n = 14$) to month 60 ($n = 3$) was 0 (0, 2.0; 95% CI − 2.2, 1.2). One participant had a decrease in Bleck score from 9 at baseline and month 18 to 4 at month 24. This was likely the result of orthopaedic surgery (bilateral 8-plate hemiepiphysiodesis in distal medial femur and right proximal tibia) 11 days before the month 24 visit; the modified Bleck score returned to 9 by the month 30 visit but decreased again to 5 at month 48 with the onset of rickets-like features on radiograph and use of a walking aid at the last visit.

Analgesic Use

The use of pain medications at baseline and during treatment with asfotase alfa is summarized in Table 4. At enrolment, 4 of the 20 participants (20%) were receiving analgesic medication and 7 (35%) had no recorded history of pain medication use. Overall, 13 participants (65%) took pain medications at some point during the MAA, with 7 of the 13 (53.8%) having stopped all analgesics at the last follow-up. No participants had a history of opioid pain medications, and participants were taking only non-opioid pain medications at last follow-up ($n = 6$).

Quality of Life (PedsQL)

Overall, participants in the analysis population aged 2 to < 18 years had PedsQL scores that indicated moderate symptoms and quality

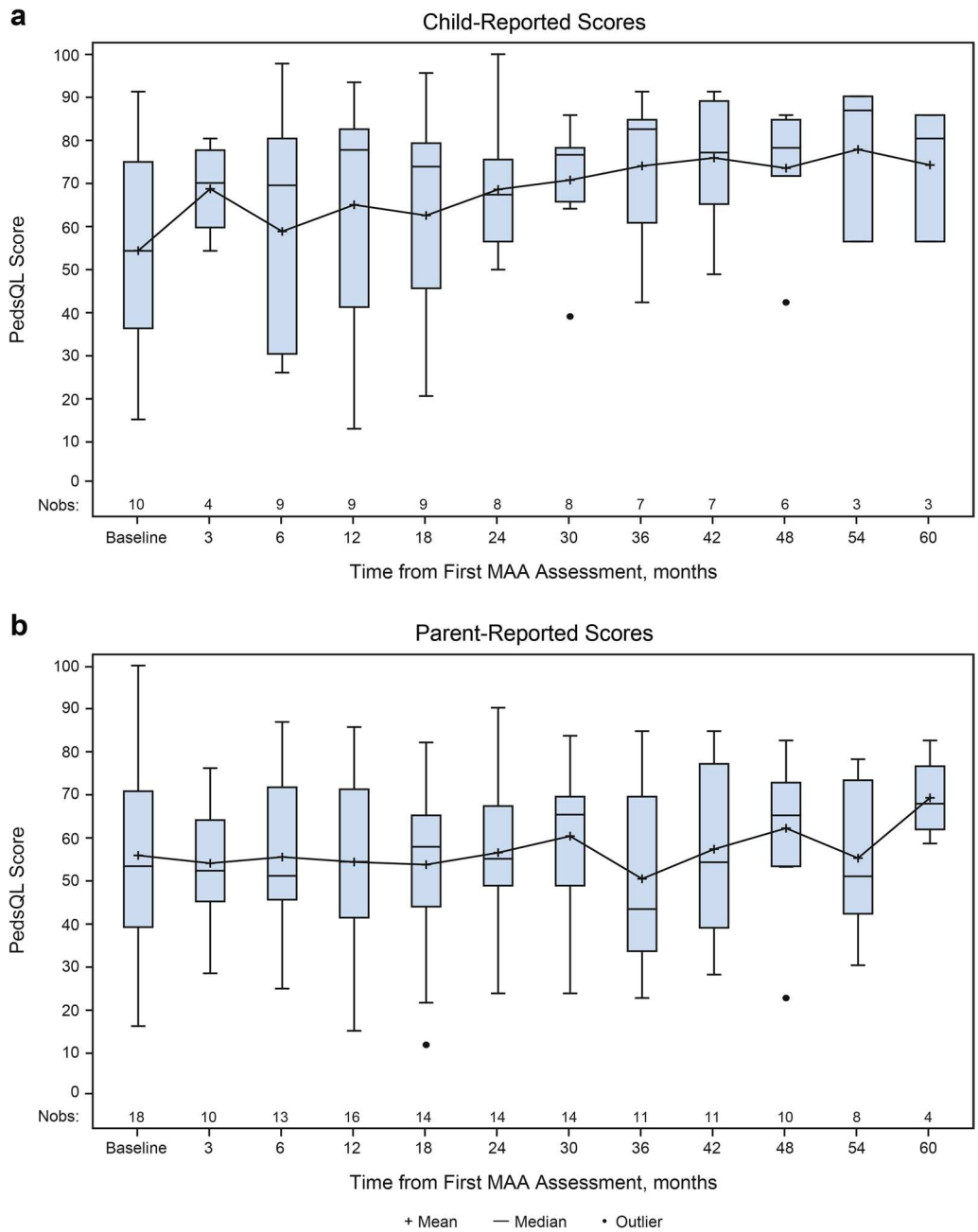

Fig. 5 Box plots showing total PedsQL utility scores over time for children 2 to < 18 years of age: **a** Child-reported and **b** parent-reported scores. Boxes represent median and interquartile range; whiskers represent minimum and maximum observations. MAA, Managed Access Agreement; Nobs, number of observations; PedsQL, Pediatric Quality of Life Inventory

of life (Fig. 5). Median (minimum, maximum) child-reported PedsQL scores were 59.2 (15.2, 91.3) at baseline ($n = 10$) and increased by 21.7 (5.4, 37.0; 95% CI: – 0.1, 44.1) at month 60 ($n = 3$). Parent-reported PedsQL scores were 53.4 (16.3, 100.0) at baseline ($n = 18$) and increased by 16.3 (9.8, 45.7; 95% CI: – 6.3,

Table 5 Adverse events of interest and serious adverse events during follow-up

	Safety population ($N = 24$) n (%)/number of events		
	Any	**Treatment related**	**Not related**
Events of interest	15 (62.5)/28	11 (45.8)/16	9 (37.5)/12
Lack of effectiveness/drug effect	2 (8.3)/2	2 (8.3)/2	0
Injection site reaction	8 (33.3)/13	8 (33.3)/13	0
Craniosynostosis	5 (20.8)/5	0	5 (20.8)/5
Injection-associated reaction	2 (8.3)/2	1 (4.2)/1	1 (4.2)/1
Neurologic event	2 (8.3)/2	0	2 (8.3)/2
Respiratory depression	1 (4.2)/3	0	1 (4.2)/3
Pneumonia	1 (4.2)/1	0	1 (4.2)/1
Serious adverse events			
Craniosynostosis	3 (12.5)/3	0	3 (12.5)/3
Infectious mononucleosis	1 (4.2)/1	0	1 (4.2)/1
Pneumonia	1 (4.2)/1	0	1 (4.2)/1
Bone deformity	1 (4.2)/1	0	1 (4.2)/1
Scoliosis	1 (4.2)/1	0	1 (4.2)/1
Petit mal epilepsy	1 (4.2)/1	0	1 (4.2)/1
Seizure	1 (4.2)/1	0	1 (4.2)/1
Dyspnoea	1 (4.2)/3	0	1 (4.2)/3
Injection site atrophy	1 (4.2)/1	1 (4.2)/1	0
Epiphysiodesis	1 (4.2)/1	0	1 (4.2)/1
Orthopaedic procedure	1 (4.2)/1	0	1 (4.2)/1

31.7) at month 60 ($n = 4$). Improvements in quality of life among treatment-experienced participants before enrolment in the MAA may have attenuated improvements in the PedsQL score during follow-up. In addition, three participants experienced adverse events unrelated to treatment that may have compromised their quality of life, possibly causing an underestimation of the clinical benefit of asfotase alfa.

Adverse Events

Nonserious and serious adverse events of interest, as well as all other serious adverse events, were recorded and are summarized in Table 5. The most common events of interest regarded by investigator assessment as related to treatment with asfotase alfa were injection site reactions (13 of 28 events in 8 of 24 participants [33.3%]). Of the 13 injection site reactions, 12 were mild and 1 was moderate in severity. Most of the events of interest (18 of 28 events [64.3%]) were mild or moderate in

intensity, and 16 of 28 events (57.1%) were considered related to treatment. A total of 16 serious adverse events occurred in 9 participants (37.5%); 1 of these events, injection site atrophy, was considered related to treatment.

DISCUSSION

Given the rarity and severity of HPP, randomized, controlled studies in patients with this disease have not been possible. Registration trials for asfotase alfa were all single-arm studies [9, 12]. The MAA was a real-world data collection project among children with HPP in the UK that presented an important opportunity to further assess the safety and effectiveness of asfotase alfa in a real-world setting. Asfotase alfa treatment demonstrated sustained effectiveness in children with HPP who were enrolled in the UK MAA and was well tolerated, with no new safety signals identified. The results of this analysis of the MAA data were consistent with those of prior studies of asfotase alfa in children with HPP, confirming the clinical benefit of this enzyme replacement therapy [9–13]. Furthermore, the results of this analysis complement those of a parallel analysis of asfotase alfa effectiveness among adults who were enroled in the UK MAA program [19], as well as results from other real-world analyses, including those from the Global HPP Registry [20, 21]. These real-world analyses provide critical evidence of treatment effectiveness during routine clinical care.

There were no deaths during up to 60 months of follow-up, despite 17 of the 20 participants in the effectiveness analysis population being < 1 year of age at the start of treatment. This result highlights the effectiveness of asfotase alfa given the high mortality rate in this population. In a retrospective chart review of untreated patients with perinatal and infantile HPP, 35 of 48 (73%) died before reaching 1.2 years of age [7]. Treatment with asfotase alfa not only helped prevent progression to death in this vulnerable population but also helped children with HPP in the MAA to maintain stable outcomes.

The majority of paediatric patients participating in the MAA were already taking asfotase alfa as part of a clinical trial or compassionate use program at the time of enrolment. Therefore, they likely had already derived much of the clinical benefit in terms of mobility, growth, and quality of life before enrolment. Consistent with this, treatment-naïve participants in the current cohort who initiated asfotase alfa at the time of enrolment in the MAA had greater improvements in height and weight *Z*-scores than those who were treatment experienced.

Treatment-naïve participants also experienced small improvements in upper and lower extremity BAMF scores, indicating improvements in mobility and gross motor skills. Improvements were also seen in treatment-experienced participants, indicating that continued treatment with asfotase alfa allowed continued clinical improvement. Maintenance of all these parameters in treatment-experienced participants during follow-up demonstrates the value of long-term use of asfotase alfa. This is also highlighted by the consistent modified Bleck scores that remained close to the maximum throughout follow-up, indicating good mobility. Similarly, improvements in 6MWT were greater than the analysis-defined MCID of 25 m, suggesting that participants improved clinically with ongoing treatment. Others have reported a validated 6MWT MCID of 31 m for children aged 5–12 years and 43 m for adolescents aged 13–17 years [22]. As with other metrics described in this report, improvements in 6MWT distance walked may have been blunted by the large number of treatment-experienced participants who were enrolled in the MAA. The results of the present study are overall consistent with data from trials in which asfotase alfa treatment improved 6MWT distance walked and percent predicted distance walked within 6 months of treatment start in paediatric, adolescent, and adult participants [11, 23].

The study population had a moderately impaired quality of life at baseline. A score of 40–70 on PedsQL indicates a moderate level of symptoms and quality of life, and a score > 70 indicates a low level of symptoms and good quality of life [24]. Median child-reported PedsQL scores at baseline were 59.2 and

parent-reported scores were 53.4, indicating that most participants had moderate symptoms of impairment at baseline, possibly indicative of their use of asfotase alfa at baseline. The median child-reported PedsQL score exceeded 70 from month 30 through the final follow-up, and parent-reported scores were > 60 at months 30, 48, and 60 in this MAA. These improvements in PedsQL during the MAA suggests that asfotase alfa results in improvements in symptom severity and quality of life. Asfotase alfa treatment similarly improved the quality of life in paediatric participants with HPP as measured by the Pediatric Outcomes Data Collection Instrument [11].

One of the principal contributors to poor quality of life in adults and children with HPP is pain [25–27]. While most children in this data collection project required analgesic support at some point during follow-up, this was not constant, and more than half of the participants who took analgesics had stopped all pain medications by the last follow-up; no participants were taking opioids at the last follow-up. Pain in patients with HPP is associated with underlying skeletal issues and physical disability [11]. The low use of analgesics and good quality of life scores during the MAA likely result from improved skeletal development and physical functioning. A previous study in children aged 6–12 years with HPP showed sustained improvements in pain, disability, and physical function throughout 5 years of asfotase alfa treatment [11].

Asfotase alfa was generally well tolerated in this population, with the most frequent adverse events related to treatment being injection site reactions. As expected, a number of serious adverse events due to the underlying disease occurred. However, only one serious adverse event, injection site atrophy, which was thought to be related to treatment with asfotase alfa, was reported. Although many participants received the recommended dose of 6 mg/kg per week, some received a higher dose in accordance with their disease manifestations, including respiratory deterioration, hypercalcaemia, severe encephalopathy, nephrocalcinosis, and poor mineralisation. Per the US prescribing information, the dose of asfotase alfa may be increased up to 9 mg/kg per week for lack of efficacy at lower doses.

Following the submission of data collected from paediatric participants during the MAA, alongside the previously conducted studies of asfotase alfa, NICE recommended asfotase alfa as a treatment option for paediatric patients with HPP [28]. Access was recommended for patients whose symptoms started before or at birth (perinatal onset) or between the ages of 0 and 6 months (infantile onset). Access was also recommended for patients whose symptoms started between 6 months and 17 years of age (juvenile onset) if (1) they were 1 to 4 years of age and had not reached expected developmental gross motor milestones for their age or were experiencing clinically significant continuing or recurring musculoskeletal pain that affected daily activities and quality of life and had not improved after two different classes of analgesic recommended by a national pain specialist or (2) they were 5 to 18 years of age and had limited mobility assessed by a specialist using the modified Bleck Ambulation Efficiency Score and a Bleck score between 1 and 6 or were experiencing clinically significant continuing or recurring musculoskeletal pain that affected daily activities and quality of life and had not improved after two different classes of analgesic recommended by a national pain specialist.

This data collection project had a number of limitations. Most children were already taking asfotase alfa at the time of enrolment; consequently, the clinical benefit observed likely reflected maintenance of the clinical benefit of asfotase alfa in this population rather than the gross clinical improvement to be expected in children initiating treatment. Another limitation is that the MAA took place during the COVID-19 pandemic, causing many participants to miss at least one functional assessment and limiting the amount of data collected.

CONCLUSIONS

This analysis of data from the MAA confirms the clinical benefit of asfotase alfa in children with HPP. Importantly, no deaths occurred, even among participants with perinatal/infantile HPP, highlighting the importance of enzyme replacement therapy in this population. Treatment-experienced participants, who represented 60% of the population in the MAA, maintained their improved clinical status, whereas treatment-naive participants had more apparent clinical improvements on treatment. Asfotase alfa was well tolerated, and no new safety signals were identified during the MAA 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. Raja Padidela: Research grant and honoraria from Alexion, AstraZeneca Rare Disease, Ultragenyx-Mereo, and Bridgebio. Nick Bishop: Investigator for Alexion, AstraZeneca Rare Disease; UK CI for Amgen; CI for Ultragenyx-Mereo; consultant for Amgen, Novo Nordisk, and Rampart; consultant and advisory board participant for Alexion, AstraZeneca Rare Disease, Ultragenyx, and Mereo; research grant from Horizon Europe. Paul Arundel: Principal investigator and advisory board participant with and recipient of honoraria from Alexion, AstraZeneca Rare Disease. Shona Fang and Alexandros Zygouras: Employees of and may own stock/options in Alexion, AstraZeneca Rare Disease. M. Zulf Mughal: Recipient of honoraria from Alexion, AstraZeneca Rare Disease and Biologix. Nick Shaw: Nothing to disclose. Vrinda Saraff: Investigator for and recipient of honoraria from Alexion, AstraZeneca Rare Disease.

Ethical Approval. Data were collected prospectively from all participants enrolled in the MAA in the UK. All enrolled participants (or

their legally authorized representative) were informed of the purpose of the data collection project and the expected use of any data collected. 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. The project was conducted in accordance with the Declaration of Helsinki. All participants consented to participate in the MAA, including completing questionnaires and attending appointments, and to have their data entered into the MAA database. The program was started in August 2017 and concluded in February 2023.

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