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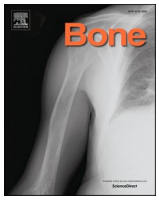

Full Length Article

Effects of asfotase alfa in adults with pediatric-onset hypophosphatasia over 24 months of treatment

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ABSTRACT

Background: Hypophosphatasia (HPP) is a rare, heritable metabolic disorder caused by deficient activity of tissue-nonspecific alkaline phosphatase (TNSALP). Asfotase alfa (AA) is a human recombinant TNSALP that promotes bone mineralization and is approved to treat eligible patients with HPP.

Methods: This prospective single-center observational study evaluated AA in adults with pediatric-onset HPP over 2 years of treatment (ClinicalTrials.gov NCT03418389). Primary outcomes evaluated physical function; secondary outcomes assessed quality of life (QoL) and pain.

Results: The study included 17 females and 5 males (mean age: 48.7 years). Median distance walked in the 6-Minute Walk Test increased significantly from baseline to 12 months ($P = 0.034$) and results were sustained. Median Timed Up and Go test time significantly decreased from baseline at 12 ($P = 0.003$) and 24 months ($P = 0.005$), as did the median chair rise time test at 12 ($P = 0.003$) and 24 months ($P < 0.002$). The change from baseline in usual gait speed was significant at 12 ($P = 0.003$) and 24 months ($P = 0.015$). Mean dominant and nondominant hand grip strength improved at 24 months ($P = 0.029$ and $P = 0.019$, respectively). Median Short Form 36 Physical Component Summary scores significantly improved from baseline at 12 ($P = 0.012$) and 24 ($P = 0.005$) months, and median Lower Extremity Functional Scale scores improved from baseline at 12 ($P = 0.001$) and 24 ($P = 0.002$) months. No significant change was noted in pain level at these timepoints. While injection site reactions occurred in 86.4 % of the participants, there were no severe side effects or safety findings.

Conclusions: Adults with pediatric-onset HPP treated with AA experienced marked improvement in functional and QoL outcomes that were observed as early as within 3 months of initial treatment and were sustained over 24 months.

1. Introduction

Hypophosphatasia (HPP) is a rare metabolic disorder caused by deficient activity of tissue-nonspecific alkaline phosphatase (TNSALP) arising from genetic alterations of the *ALPL* gene [1–3]. Resulting impairments in the turnover of phosphate-containing compounds and in the metabolism of bone minerals lead to a wide range of clinical manifestations of varying degrees of severity, with overt bone manifestations being more prevalent in more severely affected patients. In adults, these bone manifestations can include osteomalacia, deformities, and fractures/pseudofractures [2–4]. Further, adults with these manifestations consistently experience functional limitations and compromised health-related quality-of-life (QoL), as indicated by scores on the Short Form Health Survey version 2 [4].

Two related patient-reported outcomes surveys assessing burden of disease in adult patients with HPP have indicated that a high burden of disease in adulthood is associated with a substantial impact on QoL and specifically to physical ability [4]. Data from the Global HPP Registry confirmed that HPP in adults is associated with numerous clinical manifestations in multiple body systems that are associated with disability, hindered physical functioning, and psychological impairment, each having a negative impact on QoL [5]. Treatment options are largely symptomatic, aimed particularly at alleviating pain and maintaining physical function. Among adults with bone manifestations and/or accompanying osteoporosis, teriparatide has been used with inconsistent results [2,6,7]. Sclerostin inhibition has also been evaluated in

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HPP and has been shown to enhance bone formation, but not to compensate for enzyme deficiency [8].

Asfotase alfa (AA) is a human recombinant TNSALP Fc-deca-aspartate fusion protein that is designed to enable physiologic mineralization of the skeleton in patients with HPP. Pivotal trials and case reports to date have demonstrated the substantial benefit of AA treatment on survival and musculoskeletal development in infants and children [9–12]. Accordingly, following the European Medicines Agency summary of product characteristics, AA was approved to treat the bone manifestations of the disease [13].

Data from the Global HPP Registry, a repository for clinical data from patients diagnosed with HPP, confirm that many adult patients are diagnosed in adulthood, despite experiencing the onset of symptoms in childhood [14]. This analysis, based on data obtained from the observational EmPATHY study, was conducted to better understand the treatment-related effects of continuous AA treatment on functional, QoL and pain, and laboratory parameters in adult patients with pediatric-onset HPP [15–17].

2. Materials and methods

The EmPATHY study was a prospective, observational, single-center study (ClinicalTrials.gov number: NCT03418389; Evaluate and Monitor Physical Performance of Adults Treated With Asfotase Alfa for Hypophosphatasia) in adults (aged ≥18 years) diagnosed with pediatric-onset HPP who had received AA for at least 12 months in clinical practice at the Osteology Department of the University of Würzburg, Würzburg, Germany [16]. Treatment was administered per the product label at a dosage of 2 mg/kg, three times per week, with optional individualized dose adjustments after clinical risk-benefit assessments. The study design is described in Fig. 1. Initial results after 12 months of treatment have been previously reported [16]. The study design was reviewed and approved by the ethics committee of the University of Würzburg, Germany (No. 9/18) [17].

The objective of the present evaluation was to describe the effect of AA on the physical performance, QoL, and bone and mineral metabolism of adult patients with pediatric-onset HPP following 2 years of continuous treatment with AA per standard of care compared to pre-treatment baseline in patients. This evaluation included all 22 patients who received treatment with AA without any interruption.

2.1. Data collection

All assessments were conducted per the standard of care at the investigator's center. Results obtained at the last visit before any AA treatment were assigned as baseline. Participants' medical history, including HPP-related symptoms and clinical diagnoses, were obtained from medical records. After treatment initiation, subsequent onsite visits for each patient were conducted at 3 and 6 months from baseline and at 6-month intervals thereafter.

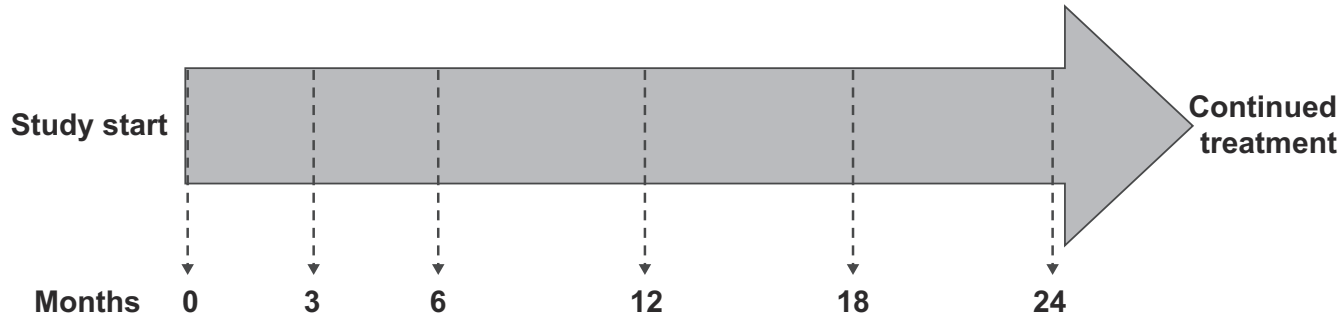
Standardized assessments, including laboratory tests and physical function and QoL measures, were conducted at every visit. Additional data collected retrospectively (i.e., through chart abstraction) and prospectively included physical examination and mobility findings and imaging studies.

2.2. Efficacy and safety variables

Clinical assessments were conducted to assess the burden of disease and its systemic manifestations and to evaluate the long-term effectiveness of AA treatment initiated in adult patients with pediatric-onset HPP as defined by standard of care.

Functional assessments, as described previously [16], included the 6-Minute Walk Test (6MWT), the Timed Up-and-Go (TUG) test, and the Short Physical Performance Battery (SPPB) consisting of a balance test, usual gait speed test, and the repeated chair rise test. Additionally, grip strength was measured using handheld dynamometry. Use of any assistive devices (e.g., crutches, walker) during completion of the 6MWT and usual gait speed test was documented.

QoL was assessed using the Short Form Health Survey version 2 (SF-36v2 German version) Physical and Mental Component Summary scores and the Lower Extremity Functional Scale (LEFS). Prevalence of current pain was measured at each visit using the following five categories: never, rarely, sometimes, frequently, persistently. If pain was present, pain intensity was quantitated on a 10-item Likert scale. Standardized laboratory testing comprising parameters relevant to HPP care were performed at the Department for Osteology (University of Würzburg) and collaborating laboratories. Laboratory data were collected through routine measurements of the following parameters: alkaline phosphatase (ALP), pyridoxal 5′-phosphate (PLP), urine phosphoethanolamine (PEA)/creatinine (Cr) ratio, parathyroid hormone 1–84 (PTH), calcium,



Assessments
(measured at all time points)

Laboratory	Functional testing	QoL and Pain
PTH, FGF-23, OC, P1NP, NTx, ALP, TRAP5b, Calcium, Phosphorous, GFR, PEA/Cr	6MWT, Gait speed, CRT, TUG, Grip strength	SF-36v2, LEFS, Pain

Fig. 1. Study design. 6MWT, 6-minute walk test; ALP, alkaline phosphatase; CRT, chair rise test; FGF-23, fibroblast growth factor 23; GFR, glomerular filtration rate; LEFS, lower extremity functional scale; NTx, N-terminal telopeptide of type 1 collagen; OC, osteocalcin; P1NP, procollagen type 1 N-propeptide; PEA/Cr, phosphoethanolamine/creatinine ratio; PTH, parathyroid hormone; QoL, quality of life; SF-36v2, short Form Health Survey version 2; TRAP5b, tartrate-resistant acid phosphatase 5b; TUG, Timed Up-and-Go test.

phosphate, fibroblast growth factor-23 (FGF-23), osteocalcin, procollagen type 1 N-propeptide (P1NP), tartrate-resistant acid phosphatase 5b (TRAP5b), and N-terminal telopeptide of type 1 collagen (NTx). Renal function/glomerular filtration rate was estimated based on serum creatinine levels, age, and sex using the MDRD formula [18].

2.3. Statistical methods

Quantitative values, including patients' age, weight, body mass index (BMI), and blood serum parameters, or scores on recorded scales administered to quantify physical or psychological conditions were assessed descriptively.

Parameters subject to inferential statistics were tested for normal distribution using the Shapiro-Wilk test. If significant deviations from normal distribution were confirmed, nonparametric methods were used for further statistical analysis. Otherwise, parametric analyses could be performed. Matched pairs *t*-test (parametric) or Wilcoxon matched pairs test (nonparametric) were performed to evaluate the difference between values at individual follow-up visits compared with baseline.

All tests were performed two sided with a significance level of 5 %. Because of the descriptive and explorative characteristic of the current study, no alpha adjustment for multiple testing was applied, and the results were interpreted accordingly. Statistical analyses were performed using SPSS Statistics 26 (SPSS Inc., an IBM company, Chicago, IL, USA).

All longitudinal assessments were restricted to data from patients without any missing values at any timepoint for the specific parameter under investigation.

Table 1
Baseline characteristics.

	Total	Females	Males
Age at treatment initiation, years			
n	22	17	5
Mean (SD)	48.7 (15.2)	51.8 (14.0)	38.4 (16.2)
Min-Max	19.0–78.0	20.0–78.0	19.0–57.0
Height, cm			
n	22	17	5
Mean (SD)	159.3 (12.2)	157.7 (8.8)	164.9 (20.6)
Min-Max	128.5–179.0	135–177.0	128.5–179.0
Weight, kg			
n	22	17	5
Mean (SD)	74.2 (21.0)	72.4 (19.2)	80.1 (28.1)
Min-Max	46.0–123.0	46.0–123.0	48.4–115.0
BMI, kg/m^2			
n	22	17	5
Mean (SD)	29.1 (6.9)	29.0 (7.0)	29.1 (7.5)
Min-Max	18.0–50.5	18.0–50.5	19.3–39.8
Baseline ALP activity, U/L			
n	22	17	5
Mean (SD)	15.6 (7.5)	11.4 (4.8)	16.8 (7.8)
Min-Max	4–31	6–18	4–31
Baseline PLP, ng/mL			
n	19	15	4
Mean (SD)	497.3 (462.1)	614.1 (608.4)	466.1 (436.3)
Min-Max	46.1–1470.0	59.5–1470.0	46.1–1365.0
Baseline PEA/Cr ratio, mmol/mol Cr			
n	18	14	4
Mean (SD)	62.1 (51.3)	49.3 (27.1)	65.8 (56.6)
Min-Max	2.2–180.0	13.5–54.9	2.1–180.0

ALP, alkaline phosphatase; BMI, body mass index; Cr, creatinine; PEA, phosphoethanolamine; PLP, pyridoxal 5′-phosphate; SD, standard deviation.

3. Results

3.1. Patient demographics and baseline characteristics

Twenty-two patients (17 females and 5 males) were included in this analysis (Table 1). The mean (SD) age at start of enzyme replacement therapy with AA was 48.7 (15.2) years (females: 51.8 years; males: 38.4 years). In 20 patients, the initial AA dosage was 6.0 mg/kg per week, and in 2 patients, the dosage was adjusted to 4.5 and 3.0 mg/kg per week. The weekly dose was administered on 3 injection days in 20 patients; of the 2 patients with dose adjustments, 1 tolerated only 2 injection days per week, and 1 had the weekly dose spread over 2 injection days.

Nineteen patients had a compound heterozygous *ALPL* genotype, 1 had a homozygous genotype, and 2 were heterozygous for dominant negative variants (patient genotype details provided in the Supplementary Table S1). Of the 22 study patients, 9 (40.9 %) had been transiently exposed to AA earlier during a phase 2 pharmacokinetics / pharmacodynamics study [15].

From baseline to 24 months in the 20 participants with available data for both timepoints, there was a significant increase in average body weight ($P = 0.001$) from 72.6 (SD, 20.9) kg to 77.6 (SD, 22.3) kg. Similarly, in those same patients, BMI increased significantly from 28.9 (SD, 6.8) kg/m^2 to 31.1 (SD, 7.3) kg/m^2 ($P = 0.004$).

3.2. History of HPP-related manifestations

All 22 patients (100 %) had skeletal manifestations of HPP: 21 had fractures, and 1 had complex bone deformities from childhood rickets without experiencing any fracture. In total, 21 patients (95.5 %) had muscular manifestations of HPP, of which 20 (90.9 %) experienced muscle weakness that limited daily activities. Overall, 21 patients (95.5) had dental manifestations, 21 patients (95.5) had a history of pain, and 8 patients (36.4 %) had a neurologic diagnosis.

3.2.1. Laboratory test results

A summary of key laboratory test findings is presented in Supplementary Table S2. By 3 months of AA treatment, PTH levels had increased significantly (Wilcoxon test $P = 0.025$); they gradually returned toward baseline values by 12 months. Subsequently, a slight increase in median PTH levels was observed, again reaching statistical significance at 24 months of treatment (Wilcoxon test $P = 0.044$) (Fig. 2A). There was no significant change in median FGF-23 level from baseline to any timepoint up to 24 months ($n = 16$; $P > 0.05$) (Fig. 2B).

In assessments of bone turnover markers, median osteocalcin (OC) levels increased significantly from baseline to 3 and 6 months ($P = 0.004$ for both) and subsequently decreased toward baseline levels beginning at 12 months, showing no significant deviations thereafter (Fig. 2C). Similarly, median P1NP levels increased significantly from baseline to 3 months ($P = 0.009$) and then decreased toward baseline levels, no longer differing significantly at any subsequent timepoint (Fig. 2D). Conversely, no significant changes were noted in median NTx from baseline to any timepoint up to 24 months (Fig. 2E). However, increases in median TRAP5b levels were significant from baseline to 3 months ($P = 0.025$) but were not significant at any other timepoint (Fig. 2F). Median serum levels for calcium and phosphorus did not show any significant changes throughout the observational period (Supplementary Table S2).

While no significant changes from baseline were noted in GFR at any timepoint up to 24 months (Fig. 3A), a significant decrease of median PEA/Cr ratio was detected at all timepoints through 24 months ($P < 0.05$ for all) (Fig. 3B). This decrease was consistent for all participants, although values showed greater interindividual variability and increasing values at subsequent timepoints. Median ALP levels were elevated, as expected, and did not change significantly over the course of treatment (Supplementary Fig. S1).

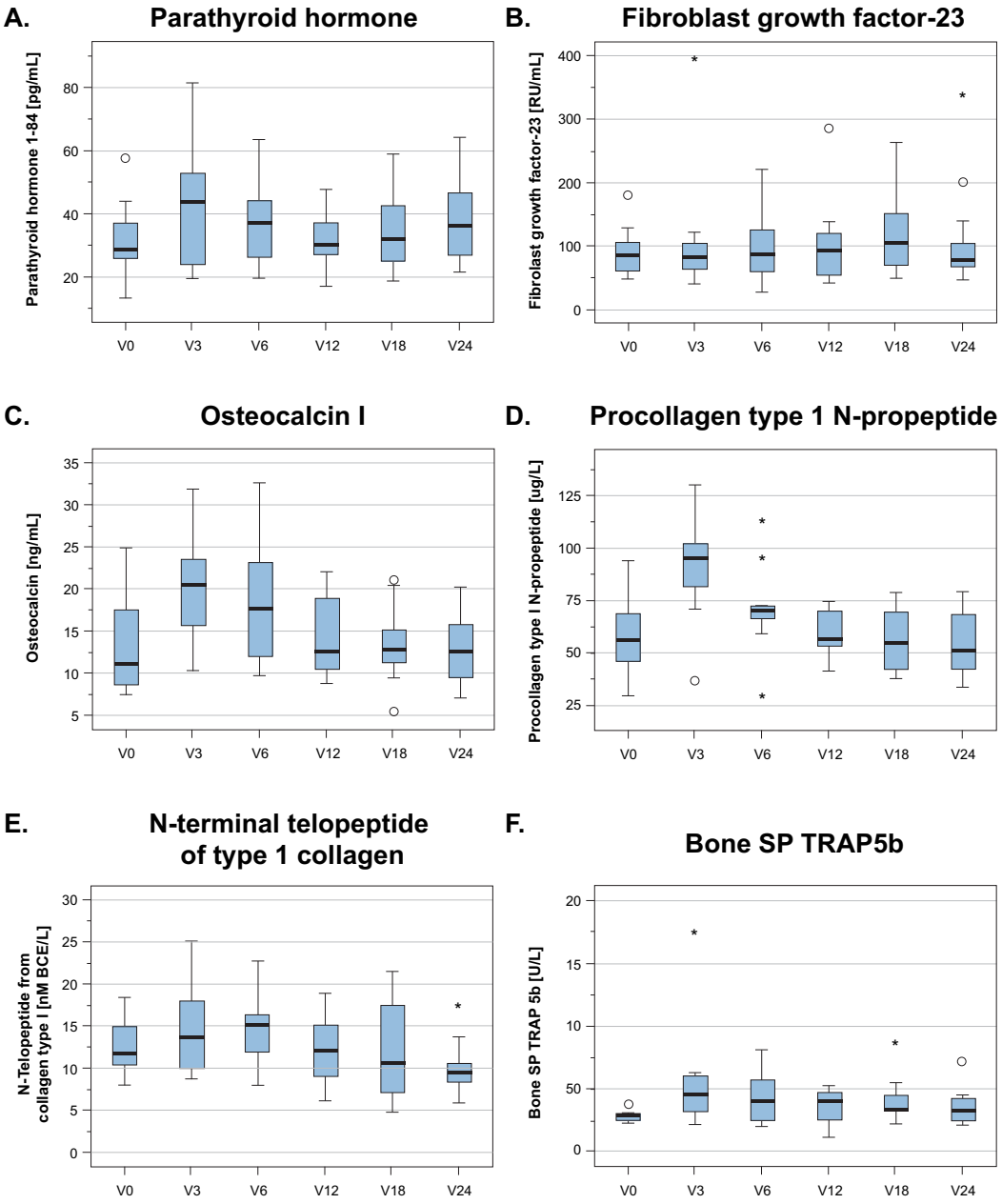


Fig. 2. Assessments of bone and mineral metabolism. Open circles indicate outliers >1.5 but <3 interquartile range above/below quartile 1/quartile 3, respectively. Extreme outliers, > 3 interquartile range above/below quartile 1/quartile 3, are indicated by an asterisk. V, visit at the specified month of treatment. Median, interquartile range, and range values are provided in Supplementary Table S3.

A) Parathyroid hormone (PTH) levels after 3, 6, 12, 18, and 24 months of treatment. Reference range: 14.9–56.9 pg/mL. Baseline to 3 months, $P = 0.025$. Baseline to 24 months, $P = 0.044$.

B) Fibroblast growth factor (FGF) levels after 3, 6, 12, 18, and 24 months of treatment. Reference range: 34–140 RU/mL (males 34–97 RU/mL; females 44–140 RU/mL).

C) Osteocalcin l levels after 3, 6, 12, 18, and 24 months of treatment. Reference range: 8.3–55.0 ng/mL (males 9.6–41.0 ng/mL; females premenopausal 8.3–34.0 ng/mL, postmenopausal 12.8–55.0 ng/mL). Baseline to 3 months, $P = 0.004$. Baseline to 6 months, $P = 0.004$.

D) Procollagen type 1 N-propeptide (P1NP) levels after 3, 6, 12, 18, and 24 months of treatment. Reference range: 13.9–85.5 μg/L (males 13.9–85.5 μg/L; females premenopausal 15.1–58.6 μg/L, postmenopausal 20.3–76.3 μg/L). Baseline to 3 months, $P = 0.009$.

E) N-terminal telopeptide of type I collagen levels after 3, 6, 12, 18, and 24 months of treatment. Reference range: 5.4–24.2 nM BCE/L (males 5.4–24.2; females premenopausal 6.2–19.0 nM BCE/L, postmenopausal 12.9–22.7 nM BCE/L).

F) Bone sialoprotein tartrate-resistant acid phosphatase 5b (Bone SP TRAP5b) levels after 3, 6, 12, 18, and 24 months of treatment. Reference range: 1.0–4.9 U/L (males 1.9–4.8; females premenopausal 1.0–4.2, postmenopausal 1.5–4.9). Baseline to 3 months, $P = 0.025$.

3.3. Assessments of physical function

3.3.1. 6-Minute Walk Test

Eighteen patients completed the 6MWT at each timepoint up to 24 months. Median distance walked increased significantly from 266 m at baseline to 347 m at 12 months ($P = 0.034$) (Fig. 4A). The improvement and absolute distances walked stabilized at 12 months, and the increases at 18 and 24 months vs baseline were not statistically significant.

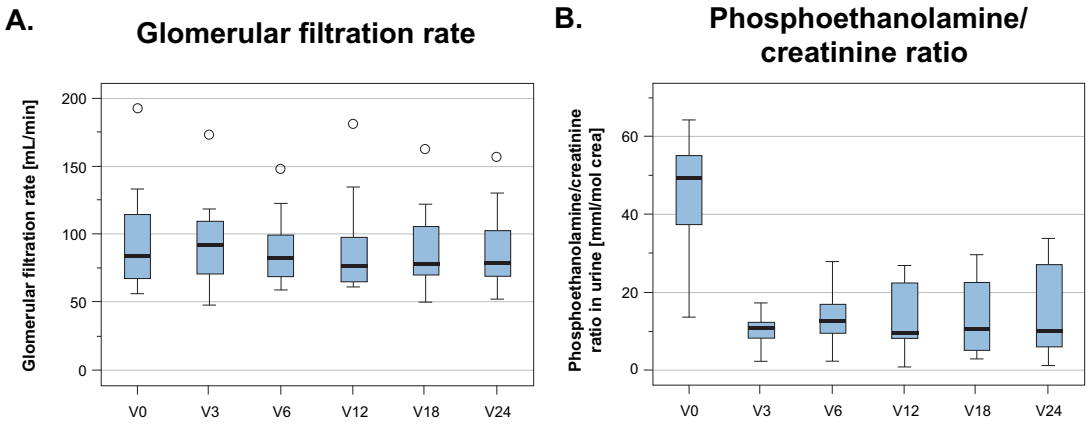


Fig. 3. Assessments of kidney function. Open circles indicate outliers >1.5 but <3 interquartile range above/below quartile 1/quartile 3, respectively. V, visit at the specified month of treatment. Median, interquartile range, and range values are provided in Supplementary Table S4.
A) Glomerular filtration rate (GFR) levels after 3, 6, 12, 18, and 24 months of treatment. Reference range: 80–140 mL/min/1.73 m^2.
B) Phosphoethanolamine/creatinine ratio after 3, 6, 12, 18, and 24 months of treatment. Reference range: 2.3–11.3 mmol/mol creatinine. Baseline to 3, 6, 12, 18, and 24 months, $P < 0.05$ for all.

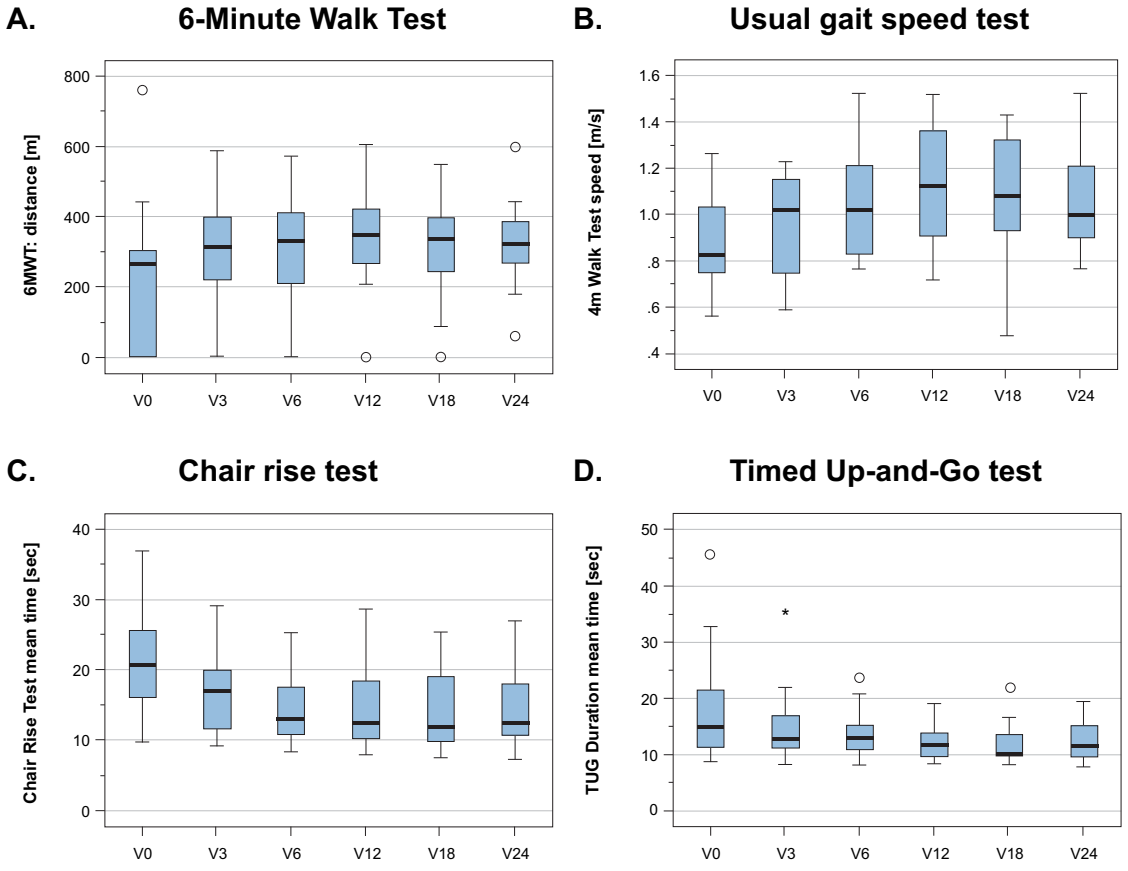


Fig. 4. Assessments of physical function. Open circles indicate outliers >1.5 but <3 interquartile range above/below quartile 1/quartile 3, respectively. Extreme outliers, > 3 interquartile range above/below quartile 1/quartile 3, are indicated by an asterisk. V, visit at the specified month of treatment. Median, interquartile range, and range values are provided in Supplementary Table S5.
A) 6-Minute Walk Test (6MWT; distance in meters [m]) after 3, 6, 12, 18, and 24 months of treatment. Baseline to 12 months, $P = 0.034$.
B) 4-m usual gait speed test speed (m/s) after 3, 6, 12, 18, and 24 months of treatment. Baseline to 12 months, $P = 0.003$. Baseline to 24 months, $P = 0.015$.
C) Repeated chair rise test time (s) after 3, 6, 12, 18, and 24 months of treatment. Baseline to 3, 6, 12, 18, and 24 months, $P < 0.05$ for all.
D) Timed Up-and-Go (TUG) test time (s) after 3, 6, 12, 18, and 24 months of treatment. Baseline to 3, 6, 12, 18, and 24 months, $P < 0.05$ for all.

Changes measured at 3 and 6 months were not significant.

3.3.2. *Short Physical Performance Battery*

Thirteen patients completed the usual gait speed test at any timepoint. The median speed to walk 4 m increased by 3 months and was sustained over the course of the study. The median usual gait speed at baseline and at 12 and 24 months was 0.82 m/s, 1.12 m/s, and 1.0 m/s, respectively. The changes from baseline in median speed to walk 4 m

were significant at 12 and 24 months ($P = 0.003$ and $P = 0.015$, respectively) (Fig. 4B). The type of walking aid required to perform the 6MWT (wheelchair, wheeled walker, or crutches) and the gait speed test improved in 8 patients (36.4 %).

The median repeated chair rise test time decreased consistently, showing improvement over the course of the study. Reductions from baseline were significant at all timepoints up to 24 months ($P = 0.005$ at 3 months, $P = 0.002$ at 6 months, $P = 0.003$ at 12 months, $P = 0.002$ at 18 months, and $P = 0.002$ at 24 months) (Fig. 4C). The median time to complete the repeated chair rise test at 12 months was similar to the time at 24 months (12.53 s and 12.48 s, respectively).

3.3.3. Timed Up-and-Go test

Eleven patients completed the TUG test at all timepoints. In general, the median TUG test time decreased over the course of treatment. Mean TUG test time at baseline, 12 months, and 24 months was 18.86 s, 12.4 s, and 12.25 s, respectively. Median TUG test time at baseline was 14.80 s and decreased and stabilized at 12 and 24 months to 11.30 s and 11.35 s, respectively. Decreases in mean TUG time from baseline were significant at all timepoints ($P = 0.021$ at 3 months, $P = 0.010$ at 6 months, $P = 0.003$ at 12 months, $P = 0.003$ at 18 months, and $P = 0.005$ at 24 months) (Fig. 4D).

3.3.4. Grip strength

Dominant and nondominant hand grip strength was assessed in 17 patients at all timepoints up to 24 months. In the dominant hand, there was a significant increase in median grip strength from baseline to 6 months ($P = 0.039$), 18 months ($P = 0.017$), and 24 months ($P = 0.029$). The change at 24 months was an approximately 15 % increase from baseline (Supplementary Fig. S2A). There was significant increase in nondominant hand median grip strength from baseline to Month 24 ($P = 0.019$). No significant difference was noted at any other timepoint (Supplementary Fig. S2B).

3.4. Health-related quality of life and pain

3.4.1. 36-Item Short Form Health Survey version 2

The 36-Item Short Form Health Survey version 2 (SF-36v2) was completed at every visit by 12 patients. The median Physical Component Summary (PCS) score was 25.18 at baseline and increased significantly to 33.96 at 12 months ($P = 0.012$) and 33.45 at 24 months ($P = 0.005$). The change from baseline to 24 months reflects a nearly 35 % improvement in median PCS score. Improvements were also significant from baseline to 3 months ($P = 0.012$), 6 months ($P = 0.034$), and 18 months ($P = 0.005$) (Supplementary Fig. S2C).

The median Mental Component Summary (MCS) score was 51.31 at baseline and increased significantly to 57.66 at 6 months ($P = 0.028$). No statistically significant changes from baseline were observed at any other timepoint, although median values remained above baseline and median MCS scores at 12 and 24 months were 55.13 and 54.37, respectively (Supplementary Fig. S2D).

3.4.2. Lower Extremity Functional Scale

Fifteen patients had Lower Extremity Functional Scale (LEFS) data at all timepoints. Median LEFS scores improved significantly from baseline (25.00) to each timepoint up to 24 months, peaking at 6 months, with scores of 44.00 at 3 months ($P = 0.022$), 50.00 at 6 months ($P = 0.006$), 49.00 at 12 months ($P = 0.001$), 45.00 at 18 months ($P = 0.002$), and 49.00 at 24 months ($P = 0.002$) (Supplementary Fig. S2E).

3.4.3. Pain

Continuous pain intensity assessments using a 10-item Likert scale without missing data were available for 9 patients. The median score was unchanged from baseline at 12 and 24 months (5.00 for all). No statistically significant change from baseline in pain level score at any timepoint was observed.

3.5. Adverse events

Across the first 24 months of treatment in the 22 patients, a total of 114 coincident medical events were documented, with 36 (31.6 %) considered possibly or likely related to asfotase alfa treatment. The 36 events included mostly reports of subjective discomfort, dysesthesia, or pain but no objectively measurable outcomes, and none were deemed severe. Coincident events also included 6 admissions for inpatient care, all for reasons not related to asfotase alfa treatment.

Injection site reactions (ISRs) were assessed separately and documented in 19 of 22 (86.4 %) patients during the first 24 months of treatment. ISRs included local pain, erythema, or persistent discoloration at the injection site. Lipodystrophy became prevalent at injection sites in 18 (81.8 %) patients over time.

4. Discussion

This observational study presents data on uninterrupted use of asfotase alfa (AA) in adult patients with HPP with a focus on consistent follow-up documentation of treatment outcomes over 24 months. Results of laboratory analyses revealed increases in bone turnover markers, specifically osteocalcin, P1NP, TRAP5b, and NTx after treatment initiation, suggesting onset of bone tissue remodeling. The occurrence of bone tissue remodeling is further supported by a transient increase in PTH which could reflect an enhanced calcium demand to recoup supposedly preexisting mineralization deficits. In line with that, a previous study focusing on bone mineral density (BMD) during AA treatment had confirmed a continuous increase of BMD over 24 months of treatment [17].

It remains speculative if the observed significant increase in body weight was a direct effect of the treatment on energy metabolism. From our observations, it seems more likely that it was an indirect result of patients' increases in appetite as a result of feeling better. Since individual weight gains were not extensive (all <10 %) and all patients claimed to be planning to revert their weight gain, we abstained from increasing the dose of asfotase alfa. Because asfotase alfa is a bone-seeking enzyme, it has been hypothesized that, particularly in obese patients, dosing might be adjusted to ideal body weight given that overall skeletal mass and volume are not essentially different in overweight patients. However, a recent pharmacokinetic data analysis from the phase 2 study of asfotase alfa in adults with HPP could not support this concept but rather confirmed the need for dosing according to actual body weight [19]. Based on these findings, there is no rationale for an absolute upper limit of dosing either.

Following treatment initiation, there was an immediate, substantial increase in serum ALP activity due to the assay also measuring the activity of the therapeutic compound. However, during the course of the study, this parameter did not exhibit any consistent pattern of variation that would render serum ALP activity a viable marker for treatment monitoring. In this regard, tests to quantify serum levels of inorganic pyrophosphate and PLP, the two well-established parameters for biochemical assessment of treatment efficacy in clinical trials, are not readily available for routine clinical use to monitor the effects of AA treatment [20]. We thus speculated that urinary PEA, which is not subject to persistent AA activity in blood samples, might be a helpful marker to monitor treatment efficacy [21]. Indeed, urinary PEA levels normalized to Cr decreased significantly and consistently in all patients. Over the course of treatment, we observed slightly increasing urinary PEA/Cr values with growing interindividual variability. Based on available data, we were not able to conclusively explain this finding, and further analyses and correlation with clinical, functional, and QoL outcomes are needed to better understand potential implications.

Regarding patients' physical performance, results of this analysis suggest that treatment with AA leads to significant improvements from baseline across various exercise capacity tests, including repeated chair rise test, TUG, usual gait speed and grip strength in adult patients with

HPP as early as and up to 2 years of treatment. Specifically, observed increase in 6MWT walking distance was statistically significant after 12 months of treatment, and the improvement appeared relatively stable, still exceeding the MCID of 31 m over the entire course of 24 months [22]. Results of the usual gait speed test, repeated chair rise test, and TUG test and assessments of grip strength in both the dominant and nondominant hand improved significantly from baseline to various timepoints over the 24-month observational period. These findings expand on the 12-month functional data from the index EmPATHY study and support the sustained effect of AA treatment in patients with HPP [16]. In the EmPATHY study, the difference from baseline in median 6MWT distance walked to 12 months was 53 m [16], which improved to 56 m at 2 years in the current study; both represent a sustained and clinically meaningful improvement in function.

Reflecting patient reported outcome, the LEFS was actually designed to assess a broad range of specifically lower extremity problems, while the SF-36 is a broad, generic measure of health status applicable to a wide range of diseases [23]. The median LEFS scores improved at 3 months and plateaued at 6 months, with increases generally sustained through 24 months of treatment. The improvement in the median LEFS scores from baseline was significant at all timepoints tested. In EmPATHY, the change in median LEFS score from baseline to 12 months of treatment was significant ($P = 0.002$) and reflects a 121 % improvement [16]. This trend was generally sustained at 24 months (approximately 95 % improvement after 2 years of treatment) and reflects a favorable effect of AA treatment which is related to patients' abilities to perform routine daily activities.

Overall, treatment with AA in severely affected patients with HPP provided rapid and sustained improvements in measures of QoL. In the current study, results showed that significant improvement in the median PCS score occurred early during treatment (as soon as 3 months) and was sustained for up to 24 months of treatment ($P = 0.005$). These results are consistent with those from the index EmPATHY study, which showed that the PCS score after 12 months of treatment improved significantly from baseline ($P = 0.01$) [16]. Results from EmPATHY also reported a 5 % improvement in the median MCS score (which includes measures of vitality, social functioning, emotional role functioning, and mental health) at 1 year of treatment [16]; this trend, although not statistically significant, was generally maintained at 2 years of treatment) [16]. However, the SF-36v2 may not accurately distinguish between the mental health status of patients with HPP compared with the general German population [24].

Owing to the observational design of this study, documentation of untoward events was based on patients' reporting and did not include systematic assessment like in an interventional study. However, the high prevalence of documented ISRs appears reassuring in terms of due diligence, and results are in line with those of previous clinical studies [15]. Most importantly, in all but 1 patient, ISRs eventually led to some kind of lipodystrophy. Otherwise, there were no severe side effects, and treatment was appropriately tolerated without any events leading to treatment discontinuation or being considered severe.

Limitations of this study include the lack of a comparator arm, interpretation was restricted to those without any missing values for any timepoint, and participants were enrolled from a single center, which may all limit the generalizability of these results. However, the effects of these limitations are somewhat mitigated because clinical care and documentation were performed in a standardized and thorough manner, which permitted analysis of outcomes in patients who had no missing data, resembling a protocolized study design.

In conclusion, adults with pediatric-onset HPP treated with AA experienced marked improvement in functional and QoL outcomes, which were observed as early as 3 months after treatment and were sustained over 24 months of treatment.

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CRediT authorship contribution statement

Lothar Seefried: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Franca Genest:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Anna Petryk:** Conceptualization, Writing – original draft, Writing – review & editing. **Marina Veith:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing.

Declaration of competing interest

Lothar Seefried is a clinical study investigator and has received consultancy fees and institutional research funding and/or grant support from Alexion, AstraZeneca Rare Disease, Boston, MA, USA.

Franca Genest is a clinical study investigator and has received speaker honoraria from Alexion, AstraZeneca Rare Disease, Boston, MA, USA.

Anna Petryk is an employee of Alexion, AstraZeneca Rare Disease, Boston, MA, USA, and may own stock/options in AstraZeneca, Cambridge, UK.

Marina Veith has no conflicts of interest to disclose.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2023.116856.

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