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Dual X-ray Absorptiometry in Children with Hypophosphatasia Treated with Asfotase Alfa: a Pooled Post Hoc Analysis

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INTRODUCTION

- Hypophosphatasia (HPP) is the rare, inherited, metabolic bone disease with systemic consequences caused by deficient tissue-nonspecific alkaline phosphatase (TNSALP) activity[1]
- Children with HPP commonly present with impaired skeletal mineralization, rickets, bone pain, fractures, premature loss of primary teeth, short stature, craniosynostosis, stiffness, muscle weakness, and reduced physical function, including compromised ambulation[1-3]
- Asfotase alfa (Strensiq®, Alexion Pharmaceuticals, Inc., Boston, MA, USA) is a human recombinant TNSALP enzyme replacement therapy approved for treatment of patients of any age with pediatric-onset HPP[4,5]
  - Children with HPP treated with asfotase alfa have shown improvements in skeletal radiographic findings, growth, strength, motor function, pain, and disability[6,7]
- In clinical studies of asfotase alfa, changes in skeletal abnormalities and mineralization defects were assessed using several modalities, including skeletal radiographs, bone biopsies, and dual x-ray absorptiometry (DXA)
  - In adults, DXA bone mineral density (BMD) measurements are used to diagnose osteoporosis and predict fracture risk[8]
  - However, in children, interpretation of DXA measurements is limited by the potentially misleading nature of areal (vs. volumetric density) BMD measurements; the impact of a growing skeleton on follow-up measurements; and lack of consensus on how to adjust for variations in bone size, body composition, and physiologic maturity[9-11]

OBJECTIVE

To understand the utility of DXA as a diagnostic tool or a way of measuring treatment efficacy in children with HPP using pooled data from 2 open-label multicenter studies of asfotase alfa

STUDIES INCLUDED

Subcutaneous Asfotase Alfa

DXA data from children with HPP from 2 open-label multicenter studies of asfotase alfa were pooled for analysis

- **Trial 1**: n=13 with evidence of HPP-related rickets on skeletal radiograph; Age 5–12 y; Dose 3–9 mg/kg/wk[a,b]
- **Trial 2**: n=6 with evidence of osteopenia on skeletal radiograph and osteomalacia by iliac crest biopsy; Age 13–18 y; Dose 2.1–6 mg/kg/wk[a,c]

N=19

Trial 1 NCT00952484, EudraCT 2015-001128-52; Trial 2 NCT01163149, EudraCT 2017-001831-38

[a]Dose changes permitted for safety or efficacy concerns. [b]6-month primary treatment period: 6 or 9 mg/kg/wk; extension phase: 3 mg/kg/wk for 3 to 9 months, then increased by protocol amendment to 6 mg/kg/wk. [c]6-month primary treatment period: 2.1 or 3.5 mg/kg/wk or no treatment (control); extension phase: 3.5 mg/kg/wk for ~6 months to 1 year, then increased by protocol amendment to 6 mg/kg/wk.

OUTCOME MEASURES

- Change from Baseline in height-adjusted BMD (BMD_{ht}) and bone mineral content (BMC_{ht}) Z-scores and absolute values for BMD and BMC assessments of the lumbar spine and whole body (including the head) measured by DXA
- Correlation between changes in DXA measures (BMD and BMC Z-scores and absolute values) and other skeletal/bone histomorphometry assessments
  - Radiographic Global Impression of Change (RGI-C) scale score[12]
  - Rickets Severity Score (RSS)[13]
  - Osteoid thickness, osteoid volume, and mineralization lag time

LIMITATIONS

- The analysis population had a wide age range and a limited number of female patients
- There was no cross-calibration of DXA scanners between participating centers; comparisons were made with each patient's Baseline data to mitigate this limitation
- DXA whole body scans included the head, which may have overestimated BMD in younger patients
- The relative contribution of asfotase alfa vs. natural accumulation of BMD due to growth in the observed improvements in DXA measures is unclear

CONCLUSIONS

- Based on the data from this pooled post hoc analysis, DXA BMD Z-scores, which are most commonly used in clinical practice, are not a useful measure of bone deficits in children with HPP either at Baseline or in response to treatment
- Other complementary measures, including functional outcomes, should be considered

RESULTS

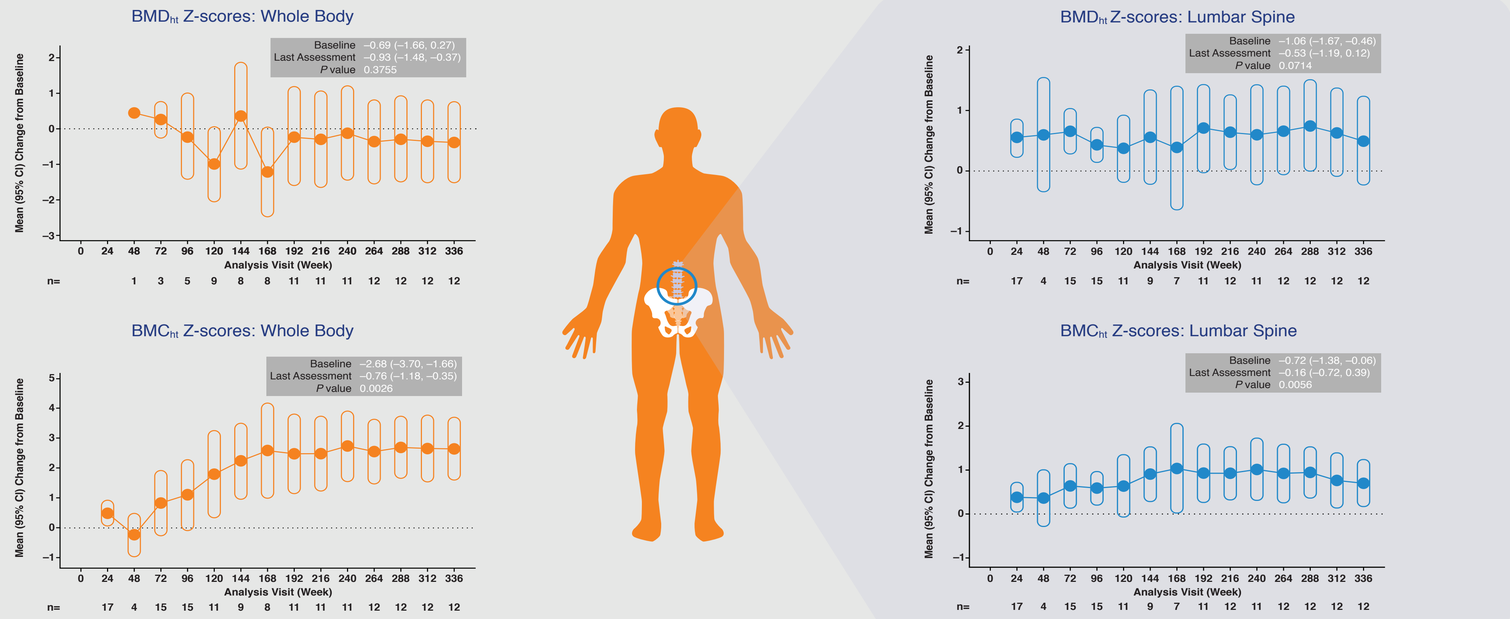
Baseline Patient Demographics and Treatment Characteristics

Characteristic	N=19
Age at enrollment, y median (min, max)	10.4 (5.9, 16.7)
Age at onset of HPP signs/symptoms, y median (min, max)	0.5 (0.0, 1.8)
Sex, n (%)	Female 4 (21.1) 15 (78.9) Male
Race, white, n (%)	17 (89.5)
Height Z-score median (min, max)	**–1.26 (–6.6, 0.0)**
Asfotase alfa treatment duration, y median (min, max)	6.3 (0.1, 6.6)
Asfotase alfa weekly total dose, mg/kg median (min, max)	5.7 (2.1, 8.4)

- 74% of patients were prepubertal
- **Baseline height Z-scores generally reflected a trend toward short stature in these patients, necessitating height adjustment of DXA Z-scores (BMD_{ht} and BMC_{ht})**
- At Baseline, only a minority of patients had whole body and lumbar spine BMD_{ht} Z-scores <–2 (17% [n=3] and 28% [n=5] of patients, respectively)

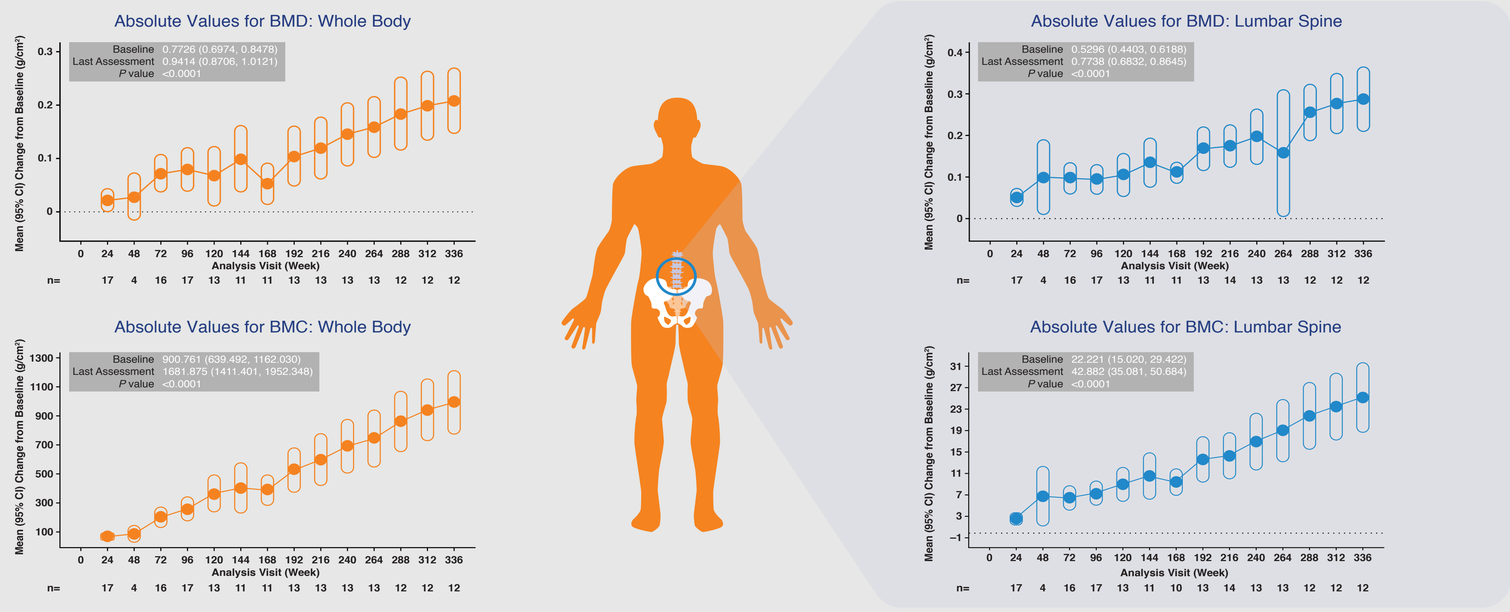
DXA Assessments

BMD_{ht} Z-scores Did Not Change, While BMC_{ht} Z-scores Increased Significantly During Asfotase Alfa Treatment



Z-scores were calculated using methods described by Zemel et al.[14] A Z-score of –2.0 or lower is considered below the expected range for age.[15] *P* values based on Wilcoxon signed-rank test comparing with 0.

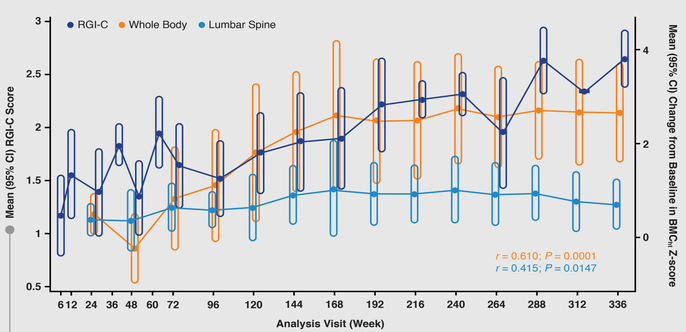
Absolute Values for BMD and BMC Increased Significantly During Asfotase Alfa Treatment



P values based on Wilcoxon signed-rank test comparing with 0.

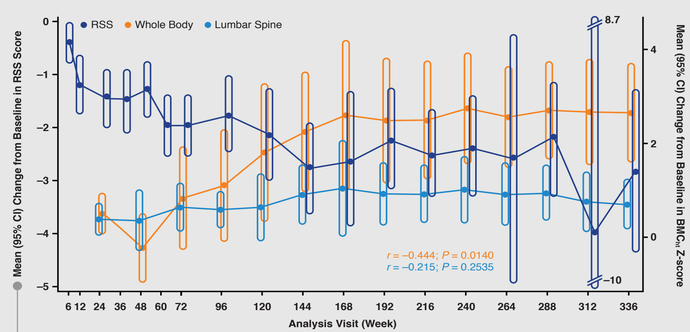
Correlation between Changes in DXA Measures and Other Skeletal/Bone Histomorphometry Assessments

Improvements in RGI-C Scores Correlated Significantly with Increases in Whole Body and Lumbar Spine BMC_{ht} Z-scores



The RGI-C is a 7-point change scale that ranges from –3 (severe worsening) to +3 (complete/ near-complete healing) used to assess radiographic changes from Baseline in the most common skeletal characteristics of HPP.[12]

Improvements in the RSS Correlated Significantly with Increases in Whole Body but Not Lumbar Spine BMC_{ht} Z-scores



The RSS is a 10-point change scale (0=absence of metaphyseal cupping and fraying [both characteristic of rickets] to 10=severe rickets; maximum of 4 points for the wrists and 6 points for the knees) originally developed to assess severity of nutritional rickets in the wrists and knees.[13]

"*r*" Values provided are Pearson's correlation coefficients (only first and last overall measurements postbaseline are included in the calculation).

- The correlation between change in lumbar spine BMD_{ht} Z-score and the RSS (r=–0.415; P=0.0225) reached significance; otherwise, there were no significant correlations between changes in whole body or lumbar spine BMD_{ht} Z-scores and the RSS or RGI-C scale scores
- The correlations between increases in absolute values of whole body and lumbar spine BMD and BMC and improvements in RGI-C scale scores were significant (all P<0.001), as was the correlation between increase in absolute value of lumbar spine BMD and improvement in the RSS (P=0.0223)
- No correlations were observed between change in any DXA measure and change in osteoid thickness, osteoid volume, or mineralization lag time

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DISCLOSURES

JHS was a clinical study investigator and received honoraria/travel support from Alexion Pharmaceuticals, Inc. ETR received consulting fees from Alexion. AP is an employee of and may own stock/options in Alexion Pharmaceuticals, Inc. SZ is an employee of Covance, Inc., and provided statistical services for this analysis under contract to Alexion. GÁM-M was a clinical study investigator and received institutional research funding and/or grant support from Alexion.

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