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Dual X-ray absorptiometry has limited utility in detecting bone pathology in children with hypophosphatasia: A pooled post hoc analysis of asfotase alfa clinical trial data

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ABSTRACT

Asfotase alfa is an enzyme replacement therapy approved for treatment of patients with pediatric-onset hypophosphatasia (HPP), a rare, inherited, systemic disease causing impaired skeletal mineralization, short stature, and reduced physical function in children. The role of dual X-ray absorptiometry (DXA) in the assessment of children with HPP has been insufficiently explored. This post hoc analysis included pooled DXA data from 2 open-label, multicenter studies in 19 children with HPP. The study population was aged ≥5 to < 18 years and had received asfotase alfa for ≤6.6 years at enrollment (male: 79%; median age at enrollment: 10.4 y [range: 5.9–16.7]; treatment duration: 6.3 y [range: 0.1–6.6]. Baseline height *Z*-scores indicated short stature (median [min, max]: −1.26 [−6.6, 0]); mean [SD]: −2.30 [1.97]), thus requiring height adjustment of DXA *Z*-scores. At Baseline, few patients had height-adjusted bone mineral density (BMD_{ht}) *Z*-scores of −2 or less for whole body ($n = 3$) or lumbar spine ($n = 5$). In treated patients, mean whole body and lumbar spine BMD_{ht} *Z*-scores did not change over time, but whole body and lumbar spine height- adjusted bone mineral content (BMC_{ht}) *Z*-scores increased significantly from Baseline to Last Assessment ($P \leq 0.0056$). Improvements in Radiographic Global Impression of Change (RGI-C) scale scores correlated significantly with increases in whole body and lumbar spine BMC_{ht} *Z*-scores ($P < 0.05$) but not BMD_{ht} *Z*-Scores. Improvements in Rickets Severity Score (RSS) correlated significantly with increases in lumbar spine BMD_{ht} *Z*-scores and whole body BMC_{ht} Z-scores ($P < 0.05$). No significant correlations were observed between any DXA and bone histomorphometry measure. These findings suggest that DXA BMD Z-scores, which are commonly used in clinical practice, have limited utility in assessing deficient bone mineralization in patients with HPP. Although BMC_{ht} *Z*-scores increased significantly over time with asfotase alfa therapy, the lack of significant changes in more than one DXA parameter suggests that this tool may not be useful in everyday clinical practice. Furthermore, the use of BMC as an independent metric is not typical or recommended by guidelines. Complementary measures, such as skeletal radiographs supplemented with age-appropriate functional assessments, should be considered.

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1. Introduction

Hypophosphatasia (HPP) is a rare, inherited, metabolic bone disease with systemic consequences caused by deficient tissue-nonspecific alkaline phosphatase (TNSALP) activity [1]. Lack of hydrolysis and accumulation of the TNSALP substrate inorganic pyrophosphate, a potent mineralization inhibitor, leads to rickets and osteomalacia in children with HPP. Other manifestations of HPP include pain, fractures, premature loss of teeth, short stature, craniosynostosis, joint stiffness, muscle weakness, and reduced physical function such as compromised ambulation [1–3].

Asfotase alfa (Strensiq®, Alexion Pharmaceuticals, Inc., Boston, MA, USA) is the only human recombinant TNSALP enzyme replacement therapy approved for treatment of patients of any age with pediatric-onset HPP [4,5]. In children with HPP, improvements in skeletal radiographic findings, growth, strength, motor function, pain, and disability have been reported with asfotase treatment [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) [6,7]. Bone mineral density (BMD) measurements are most commonly used in adults to diagnose osteopenia and osteoporosis and to predict fracture risk, and DXA is also the preferred method to assess bone density in children. Unlike in older adults, BMD in children is expressed in *Z*-score instead of T-score [8–11]. However, the interpretation of DXA measurements in children is limited by the potentially misleading nature of areal (vs. volumetric density) BMD measurements; impact of a growing skeleton on follow-up measurements; and lack of clear consensus on how to adjust for variations in bone size, body composition, growth impairment, and physiologic maturity [8,9].

Understanding of the correlation of BMD to fracture risk in a pediatric population is poor [10]. As such, the utility of DXA in children with HPP has been insufficiently explored and is also poorly understood. This post hoc analysis of pooled data from 2 open-label, multicenter studies of asfotase alfa [6,7] was conducted to understand the utility of DXA as a diagnostic tool or as a means of measuring treatment efficacy in children with HPP.

2. Methods

2.1. Study design

This is a post hoc analysis of pooled DXA data from children with HPP from 2 open-label multicenter studies of asfotase alfa (Study 1: study 006/008 [NCT00952484/NCT01203826; EudraCT number 2015–001128-52] [6]; Study 2: study 009 [NCT01163149; EudraCT 2017–001831-38] [7]) (Fig. 1). The study designs, key inclusion and exclusion criteria, and primary and secondary outcome measures for both studies have been published [6,7]. Briefly, patients eligible for this analysis were ≥5 to < 18 years of age at enrollment and had documented HPP-related rickets on skeletal radiographs (study 006/008) and osteomalacia established by iliac crest biopsy (study 009). All patients were naïve to asfotase alfa therapy at the time of enrollment. In study 006/008, patients were naïve to all bone-directed therapies, including bisphosphonates. In study 009, patients treated with bisphosphates within 2 years of study entry or for > 2 years at any time were excluded from enrollment. For patients from study 009 with prior bisphosphonate use who were enrolled, bone resorption markers had to be within normal range or elevated. Additionally, patients who received treatment with parathyroid hormone within 6 months prior to treatment with asfotase alfa were excluded from study 009. A negative result of urine pregnancy testing was required before performance of DXA for female patients of childbearing potential. Areal BMD was measured using a Hologic scanner (Hologic, Inc., Marlborough, MA, USA) at the study sites.

2.2. Study assessments

Assessments included change from Baseline in height-adjusted BMD (BMD_{ht}) and bone mineral content (BMC_{ht}) *Z*-scores and absolute BMD and BMC values for the whole body (including the head) and lumbar spine as measured by DXA. DXA was performed at Baseline and approximately every 6 months thereafter. *Z*-scores were calculated using methods and reference ranges described by Zemel et al. [12] A *Z*-score of −2.0 or lower is considered low BMD relative to age in pediatric patients [13]. Correlations between changes in DXA measures (both BMD and BMC *Z*-scores and absolute values) and changes in radiographic findings and bone histomorphometry assessments were evaluated. Assessments included (1) the Radiographic Global Impression of Change (RGI-—C) scale [14], a 7-point scale ranging from −3 (severe worsening of rickets) to +3 (complete or near-complete healing of rickets); (2) Rickets Severity Score (RSS) [15], measured on a 10-point scale (0 = absence of metaphyseal cupping and fraying to 10 = severe rickets; maximum of 4 points for the wrists and 6 points for the knees) that was originally developed to assess severity of nutritional rickets in the wrists and knees; and (3) bone histomorphometry, which included osteoid thickness, osteoid volume, and mineralization lag time. In study 006/008, bone biopsies for histomorphometry assessments were performed at Baseline and Month 6. In study 009, bone biopsies were performed at screening and Year 1 for patients randomized to asfotase alfa and at screening and Month 6 for patients initially randomized to the control group; study 009 patients initially in the control group were excluded from the bone histomorphometry correlations in this analysis.

2.3. Statistical analysis

Changes from Baseline in DXA assessments were evaluated using descriptive statistics, and *P* values were based on the Wilcoxon signed-rank test comparing with 0. For correlation between changes in DXA measures and changes in radiographic/bone histomorphometry assessments, Pearson's correlation coefficients (PCCs [*r*]) were calculated, with only the first and last overall measurements post-Baseline included in the calculation. Baseline for all patients was defined as the last assessment before the first dose of asfotase alfa.

3. Results

3.1. Patients

A total of 19 children (15 males and 4 females) with HPP were included in the analysis (13 from study 006/008 and 6 from study 009). Patient characteristics and asfotase alfa treatment exposure are shown in Table 1. The median age at enrollment was 10.4 years (range: 5.9–16.7); 74% of patients were prepubertal. The median asfotase alfa treatment duration was 6.3 years (range: 0.1–6.6).

3.2. Growth

Baseline height *Z*-scores reflected a trend toward short stature (mean [SD]: −2.30 [1.97]; median [min, max]: −1.26 [−6.6, 0]), necessitating height adjustment of DXA *Z*-scores. Median (min, max) change from baseline in height *Z*-score at Last Assessment was 0.31 (−0.9, 1.9; $P = 0.0047$). Baseline weight *Z*-score was −1.06 (−8.2, 2.3), with a change of 0.74 (−4.9, 3.4; $P = 0.0385$) at Last Assessment.

3.3. DXA measures

At Baseline, only a minority of patients had whole body and lumbar spine BMD_{ht} *Z*-scores of −2 or lower (17% [$n = 3/18$] and 28% [$n = 5/18$] of patients, respectively).

Mean whole body or lumbar spine BMD_{ht} *Z*-scores did not change during treatment with asfotase alfa; however, whole body and lumbar

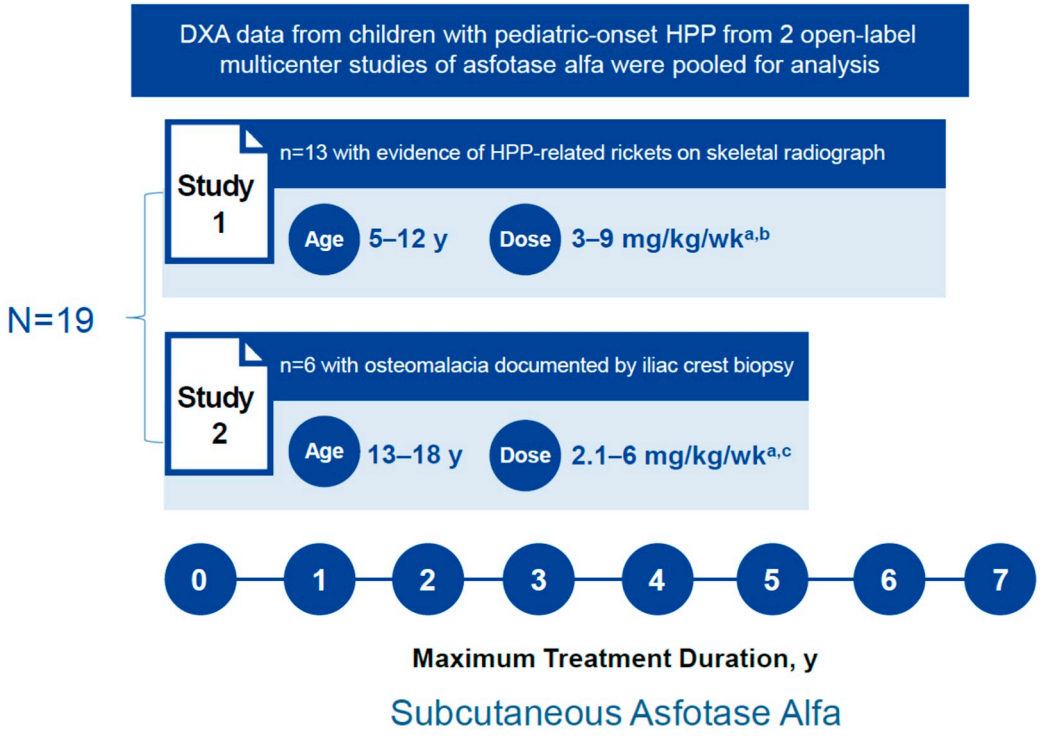

Fig. 1. Study Design. [a]Dose changes permitted for safety or efficacy concerns. [b]6-month primary treatment period: 6 or 9 mg/kg/wk.; extension phase: 3 mg/kg/wk. for 3 to 9 months, then increased by protocol amendment to 6 mg/kg/wk. [c]6-month primary treatment period: 2.1 or 3.5 mg/kg/wk. or no treatment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

Table 1
Patient characteristics and asfotase alfa exposure.

Variable	All Patients (N = 19)
Age at enrollment, median (min, max), y	10.4 (5.9, 16.7)
Age at onset of HPP clinical manifestations, median (min, max), y	0.5 (0.0, 1.8)
Race, white, n (%)	17 (89.5)
Sex, female, n (%)	4 (21.1)
Weight Z-score	
Median (min, max)	−1.06 (−8.2, 2.3)
Mean (SD)	−1.57 (2.26)
Height Z-score	
Median (min, max)	−1.26 (−6.6, 0.0)
Mean (SD)	−2.30 (1.97)
Asfotase alfa treatment duration, median (min, max), y	6.3 (0.1, 6.6)*
Asfotase alfa weekly total dose, median (min, max), mg/kg	5.7 (2.1, 8.4)

* All patients received treatment for > 2 years, with the exception of 1 patient who had a treatment duration of 1 month. No post-Baseline DXA data were collected for this patient, and as such, this patient is excluded from the analyses of change from baseline for DXA parameters.

spine BMC_{ht} Z-scores increased significantly from Baseline to Last Assessment ($P \leq 0.0056$; Fig. 2). Absolute BMD and BMC values (mean [95% CI]) for whole body and lumbar spine also increased during treatment with asfotase alfa vs. Baseline, with significant increases at Last Assessment ($P < 0.0001$) (Fig. 3). Individual BMD data (absolute BMD values and BMD_{ht} Z-scores) over time are shown in Supplemental Fig. 1.

Correlations between DXA and other skeletal parameters (RGI-—C, RSS, and bone histomorphometric assessments) were calculated to understand how well DXA compared with other assessments in measuring skeletal changes in HPP. Improvements in RGI-C scale scores correlated significantly with increases in whole body ($P = 0.0001$) and lumbar spine ($P = 0.0147$) BMC_{ht} Z-scores but not BMD_{ht} Z-Scores (Fig. 4; Supplemental Table 1). Correlations between improvements in RGI-C scale scores and increases in whole body and lumbar spine BMD and BMC absolute values were significant (all $P < 0.001$). Improvements in the RSS correlated significantly with increases in whole body BMC_{ht} Z-scores ($P = 0.0140$) and lumbar spine BMD_{ht} Z-scores ($P = 0.0225$) (Fig. 4; **Supplemental Table 1**). Improvements in the RSS were also significantly correlated with increases in lumbar spine BMD absolute values ($P = 0.0223$); however, no significant correlations with any other changes in absolute values of DXA measures was observed. No significant correlations were observed between any DXA measure and osteoid thickness ($r = -0.348$ to -0.179), osteoid volume ($r = -0.398$ to 0.065), or mineralization lag time ($r = -0.115$ to 0.006).

4. Discussion

This post hoc analysis of pooled data from 2 studies of asfotase alfa assessed the potential utility of DXA as an instrument to measure deficient bone mineralization in children with HPP. Baseline whole body and lumbar spine BMD_{ht} Z-scores were not uniformly low (−2 or lower) in children with HPP, and few patients with clear evidence of rickets on radiograph or osteomalacia by bone biopsy had low BMD Z-scores. Absolute values for BMD increased over time with asfotase alfa therapy; however, BMD_{ht} Z-scores did not change. Absolute BMC values and BMC_{ht} Z-scores increased with asfotase alfa therapy.

BMD Z-scores within a normal range have been previously reported in both children and adults with HPP [2,16–20]. In a retrospective review of data from 13 treatment-naïve children with HPP [18], whole body and lumbar spine BMD Z-scores were within the normal range, despite substantial reduction in functional exercise capacity (assessed by the 6-Minute Walk Test, which was recently validated for physical functional performance in patients with HPP [21]). In HPP, which is

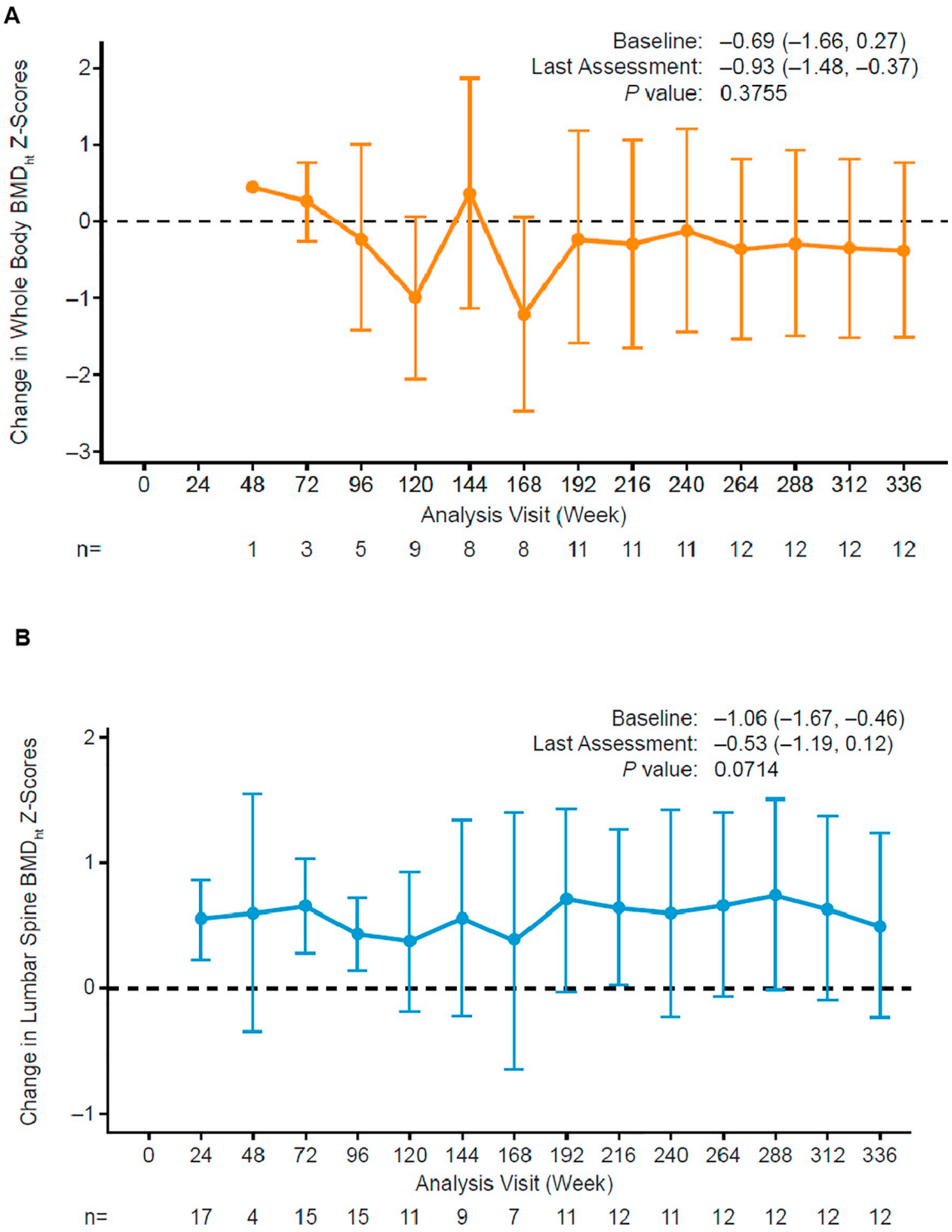

Fig. 2. Mean Change (95% CI) from Baseline in Height-Adjusted *Z*-scores for Bone Mineral Density (A: Whole Body*; B: Lumbar Spine) and Bone Mineral Content (C: Whole Body; D: Lumbar Spine). *Data for whole body BMD *Z*-scores are not available at the Week 24 visit. BMC_{ht} = height-adjusted bone mineral content; BMD_{ht} = height-adjusted bone mineral density.

characterized by impaired mineralization, a treatment such as asfotase alfa, which promotes mineralization, would be expected to increase the BMC_{ht} *Z*-score, while the lack of increase in BMD_{ht} *Z*-score could be due to the inability of DXA to properly discriminate between osteoid and mineralized bone. Additionally, as DXA assesses areal bone density, not volumetric bone density, a corresponding increase in the area involved may also explain increased BMC_{ht} Z-score with sustained BMD_{ht}*Z*-score. Lastly, significant increases from baseline in growth (both height and weight *Z*-scores) were observed at Last Assessment, which could also explain the increase in BMC_{ht} *Z*-score but not in BMD_{ht} *Z*-score.

None of the DXA measures correlated with changes in bone histomorphometry (osteoid thickness, osteoid volume, or mineralization lag time), which is the gold standard for the assessment of bone mineralization [22]. Increases in whole body and lumbar spine BMC_{ht} *Z*-scores but not BMD_{ht} *Z*-Scores correlated with improvements in RGI-C scale scores. The RGI-C scale evaluates several key radiographic

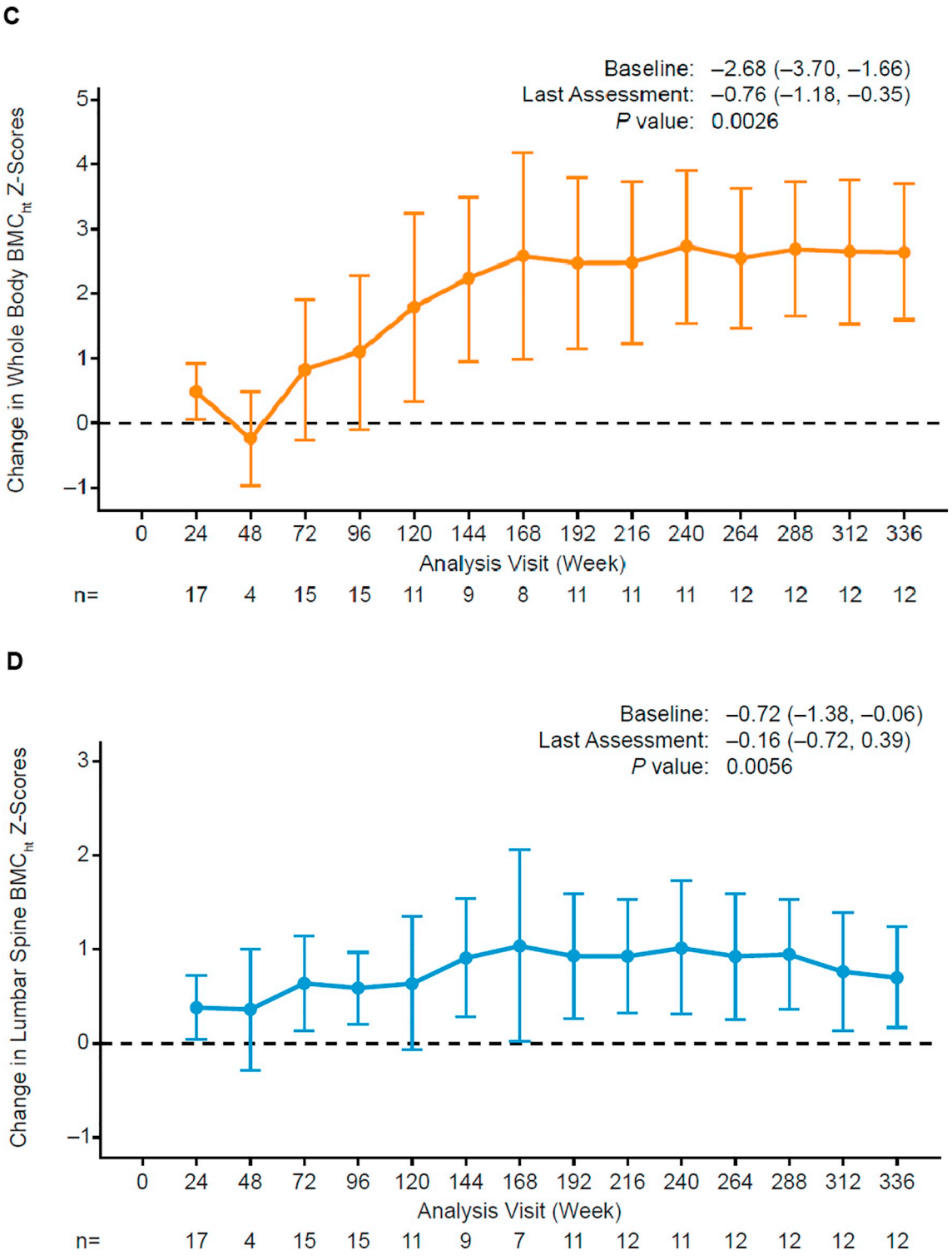

Fig. 2. (*continued*)

features of HPP, including metaphyseal flaring, fraying, radiolucencies, physeal widening, metadiaphyseal sclerosis, thin ribs, chest deformity, gracile bones, and evidence of recent fractures [14]. Increases in whole body but not lumbar spine BMC_{ht} *Z*-scores correlated with changes in RSS, and a correlation also was observed between increases in lumbar spine BMD_{ht} *Z*-score and improvement in the RSS. The lack of correlation between DXA measures and skeletal and bone histomorphometry assessments in this analysis indicates that DXA does not measure relevant parameters that are critical to understanding bone health in children with HPP (e.g., osteoid indices measured by bone biopsies, pathognomonic changes revealed by skeletal radiographs) [23], underscoring the limitations of DXA in this patient population. A recent case report of an adult with HPP treated with asfotase alfa suggests that other tools, such as high-resolution peripheral quantitative computed tomography (HR-pQCT), may be useful in assessing improvement in bone mineralization and quality indices beyond the bone mass measured by DXA [24]. However, evidence supporting the use of HR-pQCT is currently limited, as HR-pQCT is not yet clinically available. In

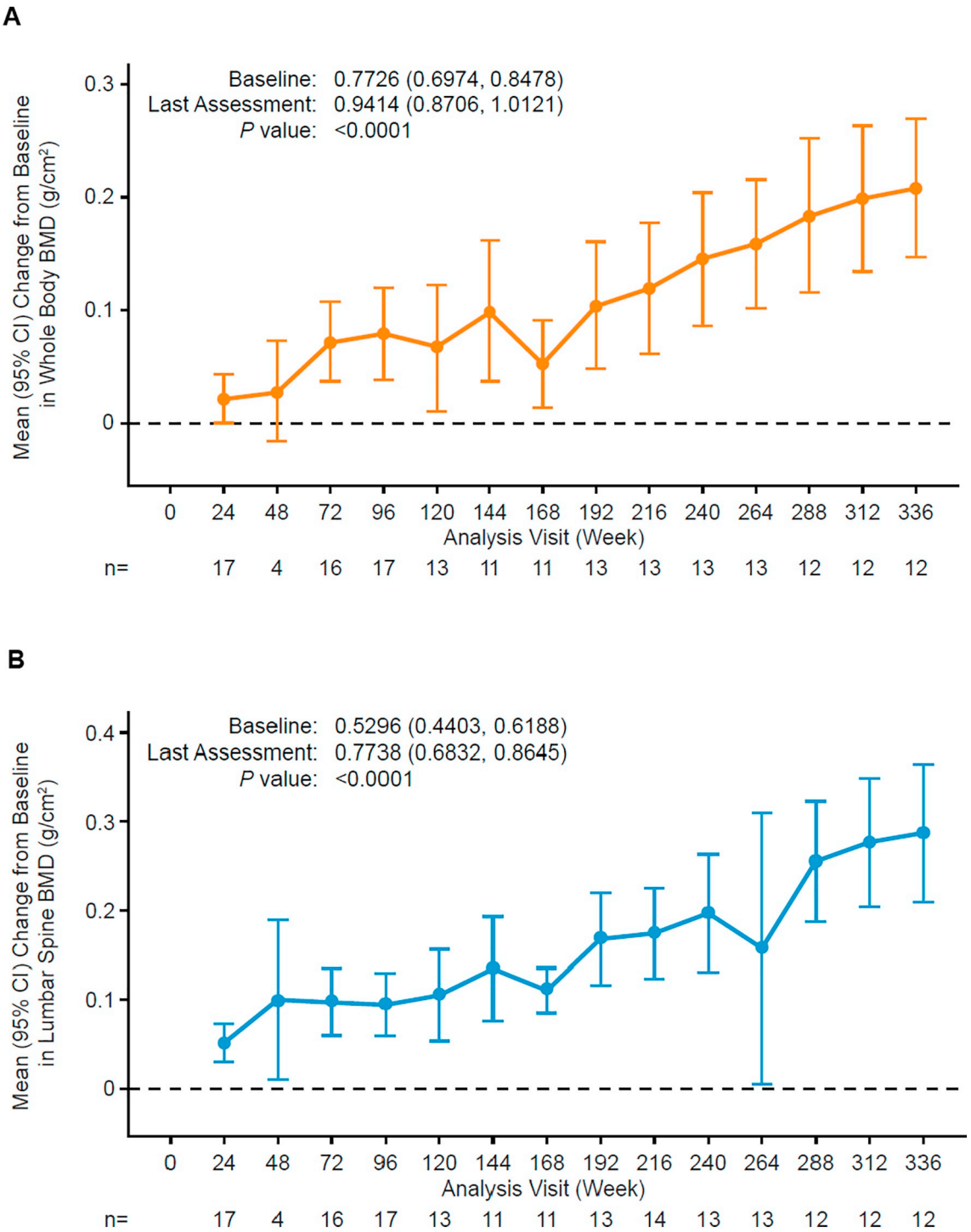

Fig. 3. Mean (95% CI) Change from Baseline in Absolute Values for Bone Mineral Density (A: Whole Body; B: Lumbar Spine) and Bone Mineral Content (C: Whole Body; D: Lumbar Spine). BMC = bone mineral content; BMD = bone mineral density.

addition, normative data for HR-pQCT measures in children are lacking, and use of this tool in children is associated with inherent challenges, such as the need for patients to remain stationary for the duration of the scan [25].

Collectively, the results of this analysis suggest that DXA measures are of limited utility in the diagnosis of HPP, assessment of disease severity, and determination of treatment efficacy. Although BMC_{ht} *Z*-scores increased significantly over time with asfotase alfa therapy, the use of BMC as an independent metric is not typical or recommended in International Society for Clinical Densitometry guidelines [11]. Additionally, whereas DXA measurements are recommended for the assessment of bone health in adults with osteomalacia or osteoporosis and in pediatric patients with diseases that affect the skeleton [11,13], previous data also suggest that DXA may not adequately measure skeletal abnormalities observed in patients with HPP [26]. A histomorphometric analysis of iliac crest biopsy samples from adults with HPP found increased trabecular number, decreased trabecular separation, increased osteoblast number and surface, and lower calcium content in patients with HPP compared with healthy controls or individuals with other types of osteomalacia [26]. It must be taken into consideration

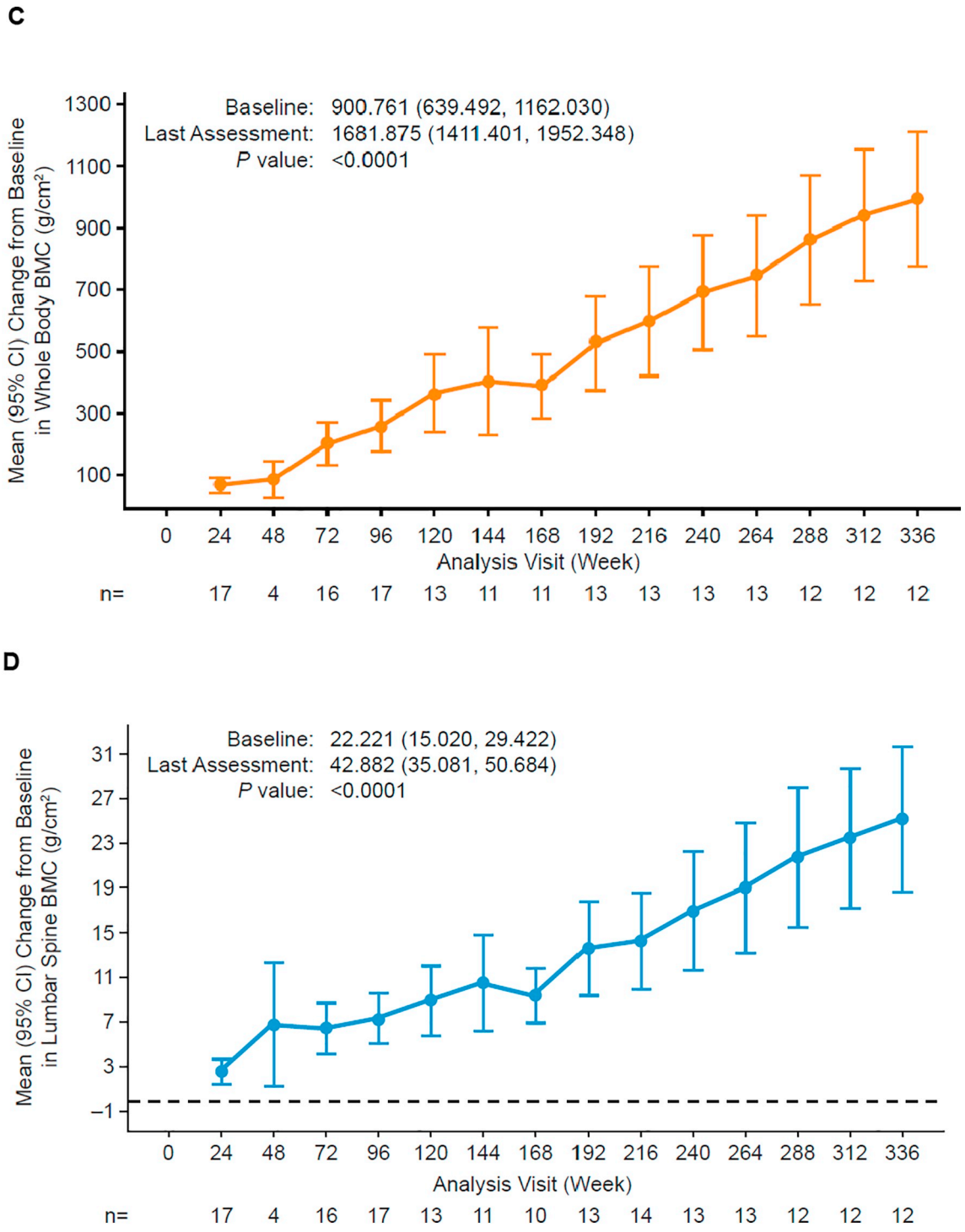

Fig. 3. (*continued*)

that the use of DXA in patients with HPP may be confounded by aberrant density readings, potentially as a result of increased proteinaceous components of nonmineralized bones or distorted bone trabeculation with areas of decreased mineralization and areas of local hypermineralization (sclerosis) [7,23,27]. Given these limitations, use of skeletal radiographs supplemented with age-appropriate functional assessments may be most useful in this patient population for assessing disease progression and/or treatment efficacy. In clinical studies, functional assessments of walking ability, gross motor function, functional disability, and pain showed impairments at Baseline that improved with asfotase alfa treatment over time [6,7]. It should be noted that while radiographs can allow for the detection of rickets, deformities, and fractures, there have been instances in adults with HPP where abnormalities detected on computed tomography scans were not readily apparent on radiographs [28]. Further, although the RSS is a metric that has been used successfully in assessing the severity of rickets [15], it is used inconsistently in clinical practice. The RGI-C was developed for and is validated in HPP [14], and as such, we view this as appropriate for assessing progression of disease in a controlled study. We acknowledge that both the RSS and RGI-C are observer-dependent and may not be ideal for use by all providers in daily clinical practice and that both scales would be useful only if patients have obvious

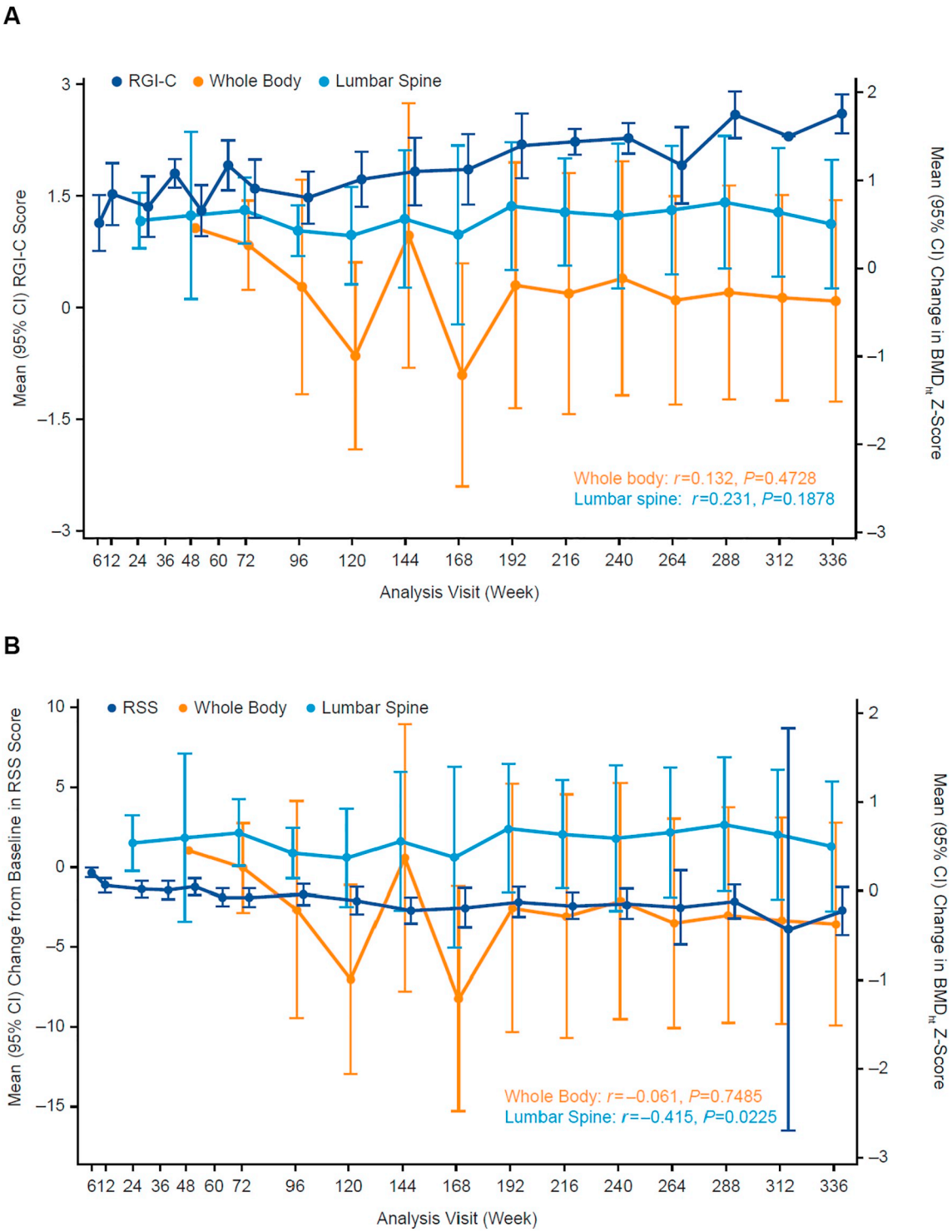

Fig. 4. Correlation of RGI-C scale scores and Change in RSS with Changes in *Z*-scores for Height-Adjusted Bone Mineral Density (A and B)* and Bone Mineral Content (C and D). "*r*" Values provided are Pearson's correlation coefficients (only first and last overall measurements postbaseline are included in the calculation). The RGI-C is a 7-point 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 [14]. The RSS is 10-point 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 [15]. *Data for whole body BMD *Z*-scores are not available at the Week 24 visit. BMC_{ht} = height-adjusted bone mineral content; BMD_{ht} = height-adjusted bone mineral density; RGI-C = Radiographic Global Impression of Change; RSS = Rickets Severity Score.

radiographic signs of rickets and open growth plates. The lack of adequate, noninvasive tools to assess bone pathology in HPP beyond the RGI-C remains a major gap and a limitation in clinical practice.

As this was a post hoc analysis, these study results have limitations. As is common in clinical studies of rare diseases, the analysis population was small and had a wide age range and a limited number of female patients. As a result of the small sample size, large variability was observed for some assessments, and small changes in BMD *Z*-score that

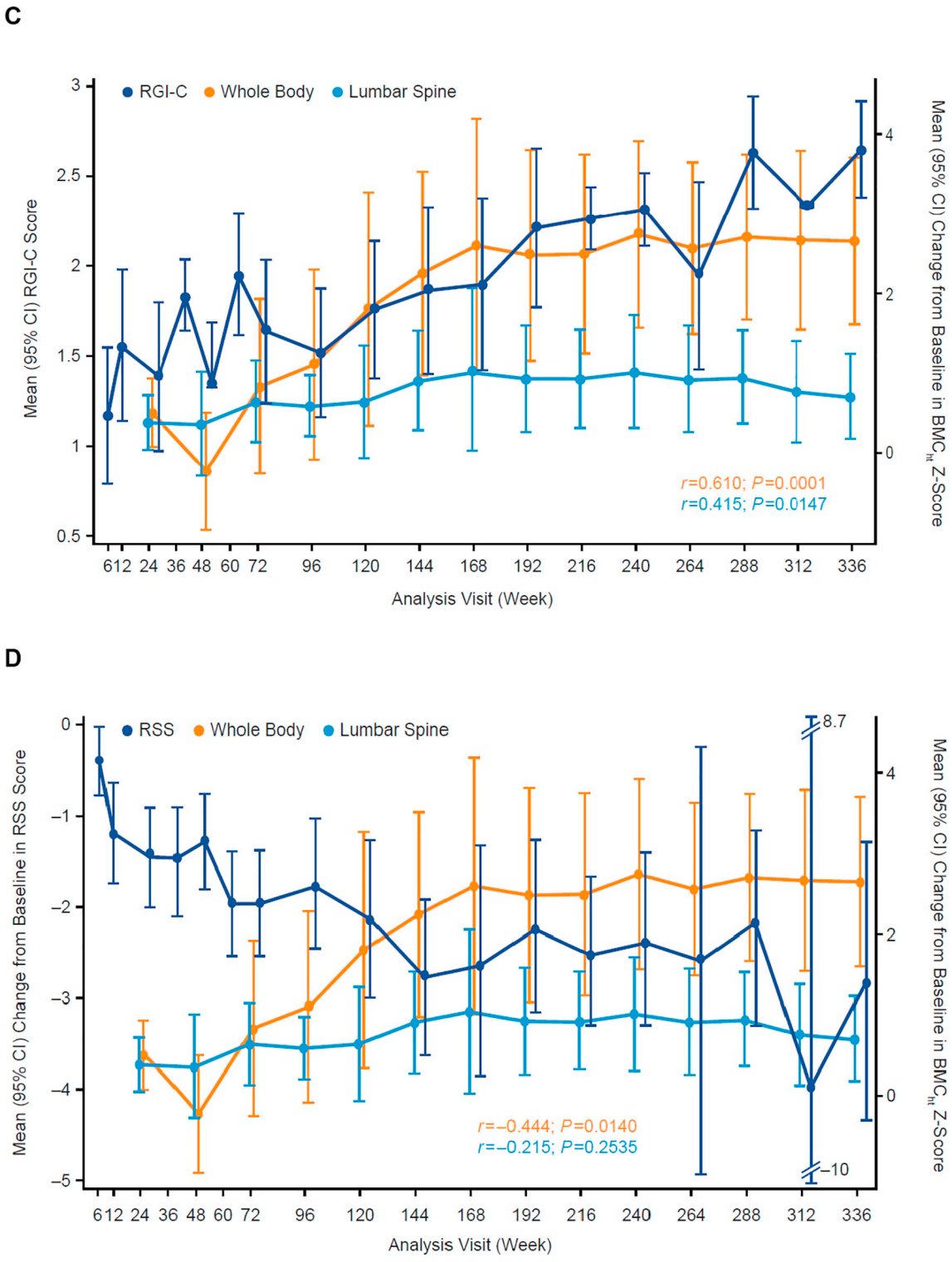

Fig. 4. (*continued*)

could still be indicative of response to therapy would likely not be detected. There was no cross-calibration of DXA scanners between participating centers; to mitigate this limitation, comparisons were made to the patient's own Baseline assessments. The whole body scan included the head, which may have overestimated BMD in younger patients. The relative contributions of asfotase alfa to the observed improvements in DXA measures versus perceived improvements due to growth-related changes in BMD are unclear. Additionally, in osteoporosis and other diseases, DXA is commonly used to evaluate and predict fracture risk by considering BMD. According to the results we have shown, and considering the phenotypic variability of the disease, the utility of DXA for fracture prediction in HPP has not been established. However, the detailed analysis of sequential evolution of other parameters measured in DXA (such as BMC) could provide some information about disease progression or asfotase alfa treatment effect. Since this study was based on data from the clinical trials and the study population was limited, it would be interesting to see in future investigations if similar observations regarding DXA measurements

before and after treatment with asfotase alfa would be made in a larger cohort of pediatric patients in a more typical clinical setting.

5. Conclusion

Based on the data from this pooled post hoc analysis, DXA BMD *Z*-scores, which are commonly used in clinical practice, are not a useful measure of bone deficits in children with HPP, either for diagnosis or monitoring treatment efficacy. Other complementary measures, including skeletal radiographs and age-appropriate functional assessments, should be considered.

CRediT authorship contribution statement

Jill H. Simmons: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization. **Gabriel Á. Martos-Moreno**: Conceptualization, Supervision, Validation, Visualization.

Acknowledgments

The authors gratefully acknowledge the contributions of the investigators who took part in the original trials that provided data for our current analysis (study 006/008 [NCT00952484/NCT01203826; EudraCT 2015-001128-52]; study 009 [NCT01163149; EudraCT 2017-001831-38]). This work was supported by Alexion Pharmaceuticals, Inc., Boston, MA, USA. Editorial and writing support was provided by Bina J. Patel, PharmD, CMPP, of Peloton Advantage, LLC (Parsippany, NJ, USA), an OPEN Health company, and funded by Alexion Pharmaceuticals, Inc.

Declaration of competing interest

JHS: Clinical study investigator; received honoraria/travel support from Alexion. **ETR:** Recipient of consulting fees from Alexion. **AP:** Employee of, may own stock/options in, Alexion. **SZ:** Employee of Covance, Inc., which provided statistical services under contract to Alexion. **GÁM-M:** Clinical study investigator; received institutional research funding and/or grant support from Alexion.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2020.115413.

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