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Clinical Research Article

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Zoledronic Acid vs Placebo in Pediatric Glucocorticoid-Induced Osteoporosis: A Randomized, Double-Blind, Phase 3 Trial

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Abbreviations: AE, adverse event; BMC, bone mineral content; BMD, bone mineral density; BS-ALP, bone-specific alkaline phosphatase; CTX, serum cross-linked C-telopeptide of type I collagen; DMD, Duchenne muscular dystrophy; DXA, dual-energy x-ray absorptiometry; GC, glucocorticoid; GIO, glucocorticoid-induced osteoporosis; IV, intravenous; LS, lumbar spine; NSAA, North Star Ambulatory Assessment; NTX, cross-linked N-teleopeptide; P1NP, N-terminal propeptide of type I collagen; PedsQL, Pediatric Quality of Life; SAE, serious adverse event; TRAP5b, tartrate-resistant acid phosphatase isoform 5b; VF, vertebral fracture; ZA, zoledronic acid.

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Abstract

Context: Glucocorticoids (GCs) prescribed for chronic pediatric illnesses are associated with osteoporotic fractures.

Objective: This study aims to determine the efficacy and safety of intravenous (IV) zoledronic acid (ZA) compared with placebo to treat pediatric GC-induced osteoporosis (GIO).

Methods: Children aged 5 to 17 years with GIO were enrolled in this multinational, randomized, double-blind, placebo-controlled phase 3 trial (ClinicalTrials.gov NCT 00799266). Eligible children were randomly assigned 1:1 to 6 monthly IV ZA 0.05 mg/kg or IV placebo. The primary end point was the change in lumbar spine bone mineral density *z* score (LSBMDZ) from baseline to month 12. Incident fractures and safety were assessed.

Results: Thirty-four children were enrolled (mean age 12.6 ± 3.4 years [18 on ZA, 16 on placebo]), all with low-trauma vertebral fractures (VFs). LSBMDZ increased from −2.13 ± 0.79 to −1.49 ± 1.05 on ZA, compared with −2.38 ± 0.90 to −2.27 ± 1.03 on placebo (least squares means difference 0.41 [95% CI, 0.02-0.81; $P = .04$]); when corrected for height *z* score, the least squares means difference in LBMDZ was 0.75 [95% CI, 0.27-1.22; $P = .004$]. Two children on placebo had new low-trauma VF vs none on ZA. Adverse events (AEs) were reported in 15 of 18 children (83%) on ZA, and in 12 of 16 (75%) on placebo, most frequently within 10 days after the first infusion. There were no deaths or treatment discontinuations due to treatment-emergent AEs.

Conclusion: LSBMDZ increased significantly on ZA compared with placebo over 1 year in children with GIO. Most AEs occurred after the first infusion.

Key Words: children, fractures, osteoporosis, glucocorticoids, steroids, zoledronic acid, Duchenne muscular dystrophy

Glucocorticoid (GC) therapy is the cornerstone of treatment for numerous pediatric diseases, including inflammatory or autoimmune disorders, and Duchenne muscular dystrophy (DMD). However, GCs increase the risk of fragility fractures, particularly at the trabecular-rich spine (1, 2). Studies have shown that the adverse impact of GC therapy on bone mineral density (BMD) occurs early in the GC treatment course (2), and that peak annual vertebral fracture (VF) incidences occur at 12 months following GC initiation in situations where the maximum annual GC exposure is in the first year (1, 3). While VFs are the main manifestation of osteoporosis in GC-treated children with inflammatory disorders (1, 2), long bone fractures are also frequent in GC-treated boys with DMD (4, 5).

Although intravenous (IV) bisphosphonates are the most commonly used drugs for the treatment of primary and secondary osteoporosis in children (6), to date there have been no randomized, placebo-controlled trials of these agents in any pediatric population with bone fragility (osteoporosis). However, nonrandomized trials of IV alendronate or pamidronate (7, 8), and a pilot, randomized, placebo-controlled pilot study of zoledronic acid (ZA) in children with Crohn disease and low bone mass (30% GC-treated) (9) showed favorable results, providing the impetus for more formal evaluation of IV ZA in GC-treated children with overt bone fragility.

IV ZA is approved globally for the treatment of osteoporosis in men, postmenopausal women, adult GC-induced osteoporosis, and for the prevention of future fractures in adults with a prior history of low-trauma hip fractures. IV pamidronate has historically been the most frequently used bisphosphonate in children (10, 11); however, in recent years ZA has been of interest given its use in adults, along with a shorter infusion time and longer duration of action compared with pamidronate.

Retrospective observational studies of IV ZA in children with GC-treated diseases and fragility fractures have shown increases in BMD parameters and absence of new VFs (12, 13). Further, in a retrospective observational study of boys with GC-treated DMD treated with IV pamidronate or ZA for 2 years, there were improvements in back pain, and stabilization or increases in the vertebral height ratios of previously fractured vertebral bodies (14). This was important, since vertebral body reshaping without bisphosphonate therapy has not previously been reported in this population. Together, these uncontrolled observations suggested IV ZA may be useful in GC-treated children with VFs, a key manifestation of GC-associated bone fragility (1, 5).

Considering the results of these studies, our goal was to formally evaluate the efficacy and safety of IV ZA in GC-treated children with fragility fractures, using a randomized, double-blind, IV placebo-controlled design. Despite the challenges of studying children in general, and rare disease in particular, this rigorous study design was particularly important in this context for three reasons. First, the efficacy of IV ZA vs placebo in children with fragility fractures remains untested in any disease context. Second, in children with transient GC exposure, the potential for medication-unassisted recovery from osteoporosis (3) dictates the need for a placebo comparison. Third, because IV bisphosphonate first-infusion side effects may mimic some of the primary disease manifestations (11, 15), there was a need to establish a framework for evaluating disease flares vs drug safety.

Materials and Methods

Study Design

This 12-month, multinational, double-blind, randomized, placebo-controlled trial was conducted in 6 countries including Canada (5 sites, 18 patients), Australia (1 site, 6 patients), the United Kingdom (2 sites, 3 patients), South Africa (1 site, 3 patients), Russia (2 sites, 2 patients), and Hungary (1 site, 2 patients). The study was first approved by the Children's Hospital of Eastern Ontario Research Ethics Board, Ottawa, Ontario, Canada (approval No. 0822E, date December 1, 2008), and then by the respective institutional review boards at each center. The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines, and the Declaration of Helsinki. The Consolidated Standards of Reporting Trials guideline was followed. The study was registered with ClinicalTrials.gov (NCT 00799266).

Participants

Children and adolescents aged 5 to 17 years with a confirmed diagnosis of nonmalignant conditions treated with systemic GC (at least one dose of IV, or oral, GC therapy within 12 months prior to screening) plus a lumbar spine (LS) BMD *z* score of less than or equal to –0.5 by dual-energy x-ray absorptiometry (DXA), and low-trauma fractures were targeted for this study. Low-trauma fracture eligibility criteria included:

- At least 1 low-trauma radiological sign of VF defined as loss of end plate parallelism, end plate interruption, or anterior cortical buckling, OR
- At least 1 low-trauma grade 1, 2, or 3 VF according to the modified Genant semiquantitative method (16), OR
- At least 1 low-trauma lower extremity long bone fracture, OR
- At least 2 low-trauma upper extremity long bone fractures

VFs were evaluated from T4 to L4 on x-rays taken within 28 days prior to randomization, and long bone fractures must have occurred within the 2 years prior to enrollment. Low trauma was defined as falling from a standing height or less. All fractures were confirmed at screening by a single radiologist through a central imaging vendor (BioClinica Inc).

Children were excluded if they had fewer than 3 evaluable vertebrae from L1 to L4 by DXA, or known primary bone disease (eg, osteogenesis imperfecta, idiopathic juvenile osteoporosis, rickets, osteomalacia). Children previously treated with antiresorptive therapy or high-dose sodium fluoride, a serum 25-hydroxyvitamin D concentration of less than 20 ng/mL (< 50 nmol/L), or a low serum ionized calcium or phosphate level were not included. Children with a history of hyperparathyroidism or hyperthyroidism within one year of screening, sarcoidosis or active uveitis, malignant neoplasms within 5 years prior to randomization, or renal impairment (estimated glomerular filtration rate < 60 mL/min/1.73 m^2) were also ineligible. Pregnancy and failure to use adequate contraception for those of childbearing potential were further exclusion criteria. Written informed consent, and assent where appropriate, were obtained from the patients, parents, or legal representatives before enrollment.

Randomization and Masking

Patients were randomly assigned 1:1 to IV ZA 0.05 mg/kg, or IV placebo, by an Interactive Web Response system (IVRS; IRT version 5.5), which was carried out by a third-party vendor (Covance IVRS and Phase Forward Oracle Health Sciences) under the direction of Novartis Drug Supply Management, independent of the study team. Randomization was carried out in blocks of 4, and stratified by baseline LS BMD *z* score categories of less than or equal to –2.0, greater than –2.0 to less than or equal to –1.0, and greater than –1.0 to less than or equal to –0.5 at screening. IV placebo and ZA were prepared in 5 mg/100 mL vials, indistinguishable from each other apart from the patients' study identification numbers. The study medication packaging was also identical for both arms. Patients, investigational staff, individuals performing the assessments, the Novartis clinical trial team and their agents, the Central Lab, the Central Imaging vendor, and data analysts were blinded to treatment allocation from the time of randomization until database lock.

Procedures

Adequate intakes of vitamin D and calcium (through diet, supplementation, or a combination of both), were mandatory starting at screening (28 days before the first infusion), and throughout the study, as follows: All children received 600 IU/day or more vitamin D, children aged 5 or older to 8 years or younger received elemental calcium 1000 mg/day, and children aged 9 or older to 17 years or younger received elemental calcium 1300 mg/day. Eligible children were randomly assigned 1:1 to receive either IV ZA 0.05 mg/kg (maximum 5 mg) or IV placebo, at baseline and at 6 months, with follow-up to 1 year. Both the drug and placebo were manufactured jointly by Novartis Pharma AG, and Fresenius Kabi GmbH.

Vertebral and Nonvertebral Fractures

The lateral and anteroposterior spine radiographs that were carried out at screening to identify VFs as part of the eligibility criteria were also used for the baseline efficacy assessment. Lateral thoracolumbar spine radiographs were repeated at month 12 to assess incident VFs. The efficacy readings for VFs were carried out according to the modified Genant semiquantitative method (16) from T4 to L4 by 2 initial readers, and a third reader resolved discrepancies between the first 2. All 3 readers were pediatric radiologists with extensive experience in VF identification in children. VFs were scored according to the following reductions in height ratios: greater than or equal to 20% and less than or equal to 25% (grade 1 [mild]), greater than 25% and less than or equal to 40% (grade 2 [moderate]), and greater than 40% (grade 3 [severe]). An incident VF was defined as a new (Genant grade 1 or higher) VF in a previously normal vertebral body. High-trauma VFs were not included in the efficacy assessments, but were recorded as adverse events (AEs) per protocol. A clinical fracture was defined as any low-trauma fracture (excluding those of the face, skull, and digits of the hands and feet) that was diagnosed following presentation to medical attention with signs or symptoms of a fracture. Radiographs from children with clinical fractures were also sent for central reading to BioClinica, Inc.

Anthropometry, Bone Age, Second Metacarpal Morphometry, Vertebral Morphometry, Dual-Energy X-Ray Absorptiometry, and Bone Turnover Markers

Height (cm) and weight (kg) were reported at baseline and at months 6 and 12. The height and weight at baseline were converted to age- and sex-matched *z* scores according to the World Health Organization reference data (WHO Child Growth References https://www.who.int/growthref/en/) (17). If a standing height could not be obtained (ie, boys with DMD), ulnar length was measured and converted to height, as previously described (18). Tanner staging by physical examination was carried out at each visit to assess physical maturity (19, 20). Radiographs of the left posteroanterior hand/wrist were taken at screening, and at month 12, for the assessment of bone age and for measurement of second metacarpal cortical thickness. Vertebral morphometry was calculated using the average ratio between the middle height and posterior height from L1 to L4 on the baseline and month 12 radiographs (21).

LS BMD and bone mineral content (BMC), total body BMC, and lateral distal femur BMD were measured at screening, month 6, and month 12 by DXA on Lunar (Prodigy, GE Lunar Corp, DPX-NT, iDXA software) or Hologic machines (fan beam scanners). DXA data acquisition and processing were managed by the central imaging vendor (BioClinica Inc). DXA machines of a given manufacturer were cross-calibrated using a BonaFide Phantom. LS BMD *z* scores were generated using manufacturer-specific databases (version 13.1 for Hologic, version 8.0 for Lunar). Raw results were combined for final reporting and analysis, as were *z* scores.

Serum bone biomarkers (overnight fasting samples) were also measured at baseline, 6 and 12 months, and included cross-linked N-teleopeptide (NTX, OSTEOMARK, Wampole Laboratories), bone-specific alkaline phosphatase (BS-ALP, OSTASE, Beckman Coulter), serum N-terminal propeptide of type I collagen (P1NP, Total PINP, Roche Diagnostics), and tartrate-resistant acid phosphatase isoform 5b (TRAP5b, Bone TRAP Assay Kit, SBA Sciences).

Pain, Quality of Life, and the North Star Ambulatory Assessment

Pain was measured according to the Faces Pain Scale–Revised at months 3, 6, 9 and 12 (22). Quality of life was evaluated by the Pediatric Quality of Life (PedsQL) 4.0 questionnaire (23) at baseline and 12 months. For boys with DMD, the North Star Ambulatory Assessment (NSAA) was carried out as an indicator of muscle strength at baseline and 12 months (24).

Safety Assessments

All AEs and serious AEs (SAEs) were monitored and recorded. Laboratory biochemistry, hematology, and physical examinations were performed at screening, and at each dosing visit. An increase in the serum creatinine by 44.2 µmol/L (0.5 mg/dL) or more between the screening and randomization visits met withdrawal criteria. Serum

creatinine was monitored by the local laboratory at screening for eligibility, and immediately prior to each infusion; if abnormal, the infusion was delayed until normalization. Serum ionized calcium was also measured at pre dose, and at 24 and 48 hours post dose via the local laboratory. In addition, serum calcium, phosphorus, estimated glomerular filtration rate, and a urinalysis were analyzed in a central laboratory 10 days after each infusion; phosphorus was also measured at screening. The postinfusion laboratory investigations were chosen at 24 and 48 hours for serum calcium given the need to monitor for acute changes in this mineral ion that could potentially herald serious hypocalcemia-related symptoms. The remaining postinfusion investigations, including serum calcium, were measured at 10 days following each infusion to detect persistent changes that would potentially require follow-up by the site investigators prior to the next infusion.

Outcomes

The primary end point was the superiority of ZA vs placebo with respect to the change in LS BMD *z* score from baseline to 12 months. The secondary outcomes compared to baseline included LS BMD *z* score at 6 months, LS and total body BMC at 6 and 12 months, serum bone turnover markers at 6 and 12 months, new VFs, vertebral morphometry and second metacarpal cortical width at 12 months, and pain according to the Faces Pain Scale–Revised at 3, 6, 9, and 12 months. ZA urinary concentrations were measured on an overnight sample, or on a sample that occurred over at least 4 waking hours (both at 12 months). Exploratory outcomes compared to baseline included distal femur BMD percentage change at 6 and 12 months, changes in height at 6 and 12 months (absolute and *z* scores), new clinical fractures, the PedsQL 4.0 score at 12 months, and the NSAA total score at 12 months (the latter for boys with DMD only).

Statistical Analysis

The study was powered to assess the between-group changes in LS BMD *z* score from baseline to 12 months, assuming a 0.63 increase over 12 months with ZA vs no change in the *z* score in the placebo group, and a common SD of 0.93. The power calculation was based on observations from a nonrandomized, case-control trial of pamidronate in GC-treated children with renal and rheumatic disorders by Acott et al (8). With these assumptions, an end-of-study sample size of 82 patients was required to provide 85% power at the significance level of .05. Adjusting for a dropout rate of 10%, a total of 92 patients were targeted for random assignment.

All children were included in the safety analyses. Efficacy end points were analyzed on a modified intention-to-treat population, defined as children who had evaluable baseline and at least one available, postbaseline (month 6 or 12) LS BMD *z* score assessment. BMD, BMC, vertebral morphometry, second metacarpal width, height, and $\log_e$-transformed bone turnover markers were assessed based on analysis of covariance models with treatment, pooled centers, underlying conditions treated with GC, and the corresponding baseline value as explanatory variables, and pooled centers as a random effect. Missing data for the primary efficacy end point were imputed using last observation carried forward. Given the underestimating effect of short stature on areal BMD, the LS BMD *z* scores (the primary outcome) were adjusted for height *z* scores as a post hoc analysis (25). Results were presented as least squares mean, least squares mean changes from baseline with SE, and the differences in least squares mean changes from baseline between groups with 95% CI. For bone turnover markers, a $\log_e$ transformation of the values at each visit was used to normalize the distribution of results.

The statistical analysis was carried out using SAS software version 9.1. A data monitoring committee was implemented to safeguard patient safety; all committee members were independent of the sponsor and study investigators, and regularly reviewed the safety data.

Results

GC-treated children with bone fragility were recruited to the study between December 4, 2008 and March 5, 2018. Of the 274 children screened, 34 met the eligibility criteria and were enrolled in the study. The reasons for screen failures and the disposition of patients are described in Fig. 1.

The majority of children enrolled were White (27/34, 79%), boys (23/34, 68%), and were between ages 9 and 17 years (29/34, 85%). The population included children with rheumatic conditions (12/34, 35%), inflammatory bowel disease (9/34, 26%), and DMD (13/34, 38%). Table 1 describes the baseline clinical characteristics in each group. Sixty-one percent (11/18) of the children in the ZA group received at least one dose of GC for the treatment of their underlying disease between baseline and 12 months, compared with (4/16) 25% on placebo. All children were enrolled after meeting the VF criteria; none were enrolled on the basis of low-trauma long bone fractures.

For the primary end point at month 12, children on ZA had greater improvements in LS BMD *z* score compared with placebo (mean ± SD increase from −2.13 ± 0.79 at baseline to −1.48 ± 1.08 at 12 months on ZA, compared with −2.38 ± 0.90 to −2.33 ± 1.03 on placebo; least squares mean difference 0.43; 95% CI, 0.03-0.83;

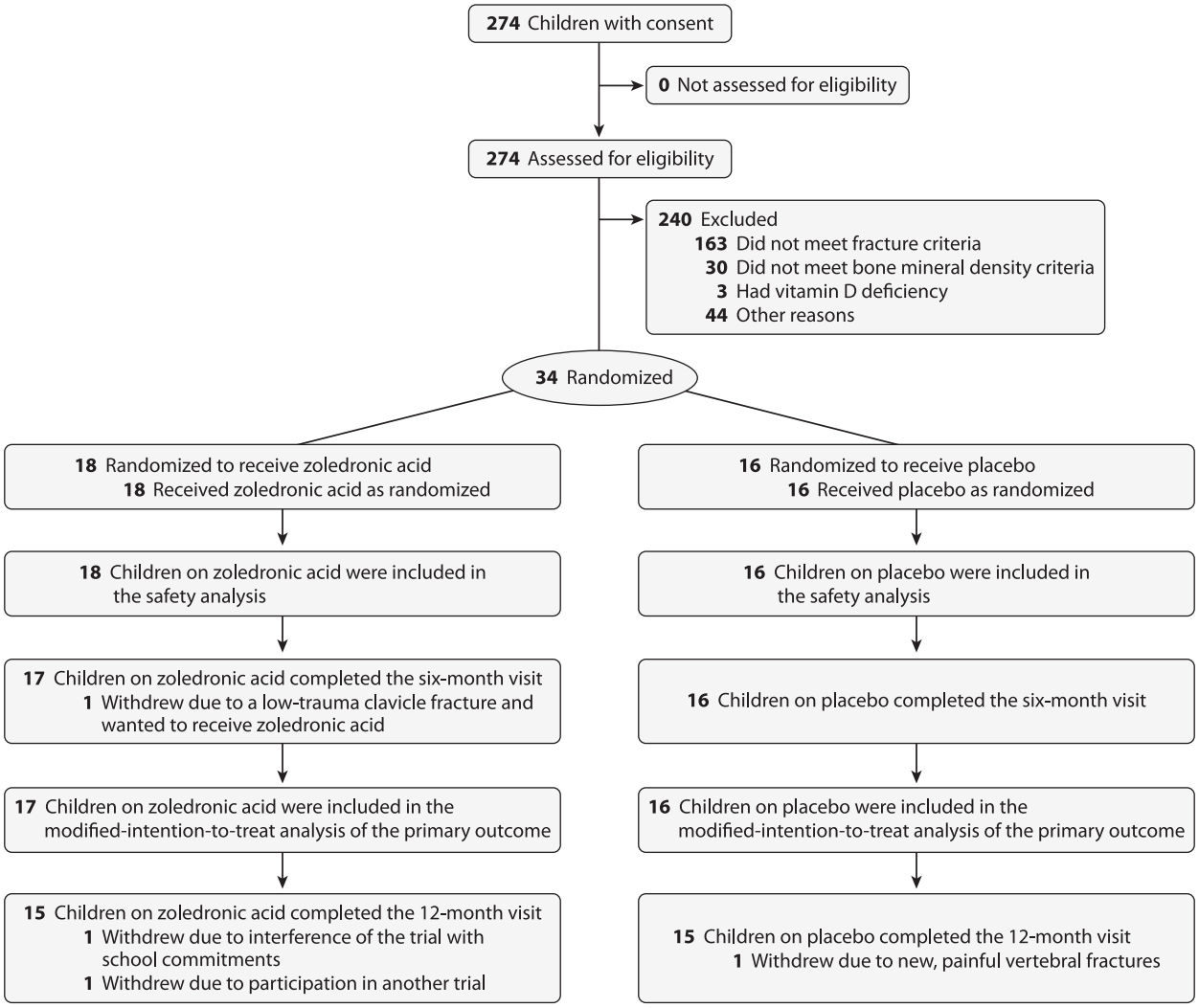

Figure 1. Disposition of patients.

$P = .04$) (Fig. 2A). When corrected for height z score, the least squares means difference in LS BMD z score was 0.75 (95% CI, 0.27-1.22; $P = .004$) (Fig. 2B). Almost three-quarters (73.6%) of the 1-year change in LS BMD z score occurred in the first 6 months; however, neither the change from baseline in LS BMD z score, or height z score-adjusted LS BMD z score, reached statistical significance until 12 months. There were nonsignificant increases in LS and total body BMC, and in distal femur BMD, on ZA compared with placebo (Fig. 2C-2E). Similarly, there were no significant differences between the 2 groups for changes in height, vertebral morphometry at L1 to L4, or second metacarpal morphometry (Table 2).

None of the children on ZA had new low-trauma VFs, compared with 2 children on placebo. Two children on placebo had a single, incident thoracic VF each (one grade 1, and the other grade 2). One patient on ZA had a low-trauma clavicle fracture, and 2 patients in each group had fractures of unknown trauma (a tibia fracture on ZA, and a wrist fracture on placebo). The Kaplan-Meier estimates of the clinical fracture cumulative incidence was 73% (95% CI, 42.8-102.2) on ZA and 82% (95% CI, 59.8-103.7) on placebo.

In the placebo group, bone turnover markers increased (NTX, PINP, and BS-ALP), or remained stable (TRAP5b), whereas all but TRAP5b declined significantly on ZA compared with placebo (Fig. 3). At month 12, samples were below the limit of quantitation (< 36.8 nmol/L or < 10 ng/mL) for the urinary concentration of ZA, in the 3 patients who consented to this part of the study. Changes in pain are reported in Table 3, and the exploratory changes from baseline to 12 months in the PedsQL and NSAA total scores are presented in Table 4.

Safety Outcomes

There were no deaths, nor treatment discontinuations due to AEs or SAEs, other than children who discontinued

Table 1. Patient baseline demographic and clinical characteristics (in the intention-to-treat population[a])

Characteristic	Zoledronic acid (n = 18)	Placebo (n = 16)
Age, mean ± SD, y	13.0 ± 3.5	12.3 ± 3.4
Median (Q1-Q3)	14.5 (9.0 to 16.0)	12.5 (10.0 to 15.0)
Bone age, mean ± SD, y	13.2 ± 3.9	11.1 ± 3.3
Median (Q1-Q3)	13.5 (10.8 to 15.3)	12 (8.9 to 13.3)
Boys, n (%)	12 (67)	11 (69)
Girls, n (%)	6 (33)	5 (31)
White, n (%)	13 (72)	14 (88)
Diagnosis, n (%)		
Duchenne muscular dystrophy	6 (33)	7 (44)
Rheumatic disorders	5 (28)	7 (44)
Crohn disease	7 (38.9)	2 (13)
Height *z* score, mean ± SD	–1.0 ± 1.4	–1.5 ± 0.9
Median, g	–0.7 (–1.4 to –0.3)	–1.6 (–2.0 to –0.9)
Weight *z* score, mean ± SD	–0.1 (1.8)	–0.5 (1.2)
Median, g	–0.3 (–1.0 to 0.7)	–0.6 (–1.2 to 0.3)
Pubertal stage, n (%)		
Stage I/II	8 (44)	12 (75)
Stage III/IV/V	10 (56)	4 (25)
Serum 25(OH)D, mean ± SD, nmol/L	70.4 ± 18.9	76.3 ± 26.6
Median, g	69.0 (55.0 to 84.0)	80.5 (50.0 to 95.5)
LS BMD *z* score, mean ± SD	–2.1 ± 0.8	–2.4 ± 0.9
Median (Q1-Q3)	–2.0 (–2.5 to –1.6)	–2.3 (–3.1 to –1.7)
LS BMC, mean ± SD, g	30.9 ± 15.2	22.6 ± 6.6
Median (Q1-Q3)	27.6 (18.0 to 44.7)	22.0 (18.1 to 27.4)
Total body BMC, mean ± SD[b], g	1507.3 ± 600.3	1050.6 ± 253.1
Median (Q1-Q3)	1479.5 (938.1 to 1953.8)	1072.0 (826.9 to 1227.3)
Distal femur BMD, mean ± SD[c], g/cm^2	0.8 ± 0.3	0.6 ± 0.3
Median (Q1-Q3)	0.7 (0.6 to 1.1)	0.6 (0.5 to 0.9)
Vertebral morphometry (average mid-to-posterior height ratio L1-L4), mean ± SD[d]	1.0 ± 0.0	1.0 ± 0.1
Median (Q1-Q3)	1.0 (1.0 to 1.0)	1.0 (1.0 to 1.0)
Second metacarpal cortical width, mean ± SD[e], mm	0.4 ± 0.2	0.4 ± 0.1
Median (Q1-Q3)	0.3 (0.3 to 0.4)	0.4 (0.3 to 0.5)
Vertebral fractures, n (%)	18 (100)	16 (100)
Genant classification		
Grade 1 (as worst grade), n (%)	13 (72)	9 (56)
Grade 2 (as worst grade), n (%)	3 (17)	2 (13)
Grade 3 (as worst grade), n (%)	1 (6)	1 (6)
Radiological signs of fracture		
Loss of end plate parallelism, end plate interruption, or anterior cortical buckling, n (%)	1 (5)	4 (25)
Average No. of vertebral fractures per patient, mean ± SD	2.7 ± 2.2	3.1 ± 2.4
Median (Q1-Q3)	2.0 (1.0 to 3.0)	2.0 (1.0 to 4.0)
Low-trauma, upper or lower extremity long bone fractures, n (%)	0.0 (0)	0.0 (0)
Faces Pain Score–Revised (out of 10), mean ± SD[f]	1.2 ± 1.7	1.9 ± 1.9
Median (Q1-Q3)	0.0 (0.0 to 2.0)	2.0 (0.0 to 4.0)
PedsQL score, mean ± SD	34.7 ± 14.3	41.4 ± 12.6
Median (Q1-Q3)	41.0 (20.0 to 44.0)	44.0 (33.0 to 51.0)

Abbreviations: BMC, bone mineral content; BMD, bone mineral density; LS, lumbar spine; PedsQL, Peds Quality of Life; Q, quartile; 25(OH)D, 25-hydroxyvitamin D.
[a]Intention-to-treat population = all children who underwent random assignment.
[b]n = 17 for zoledronic acid and n = 14 for placebo.
[c]n = 11 for zoledronic acid and n = 10 for placebo.
[d]n = 10 for zoledronic acid and n = 13 for placebo.
[e]n = 9 for zoledronic acid and n = 12 for placebo.
[f]n = 15 for placebo.

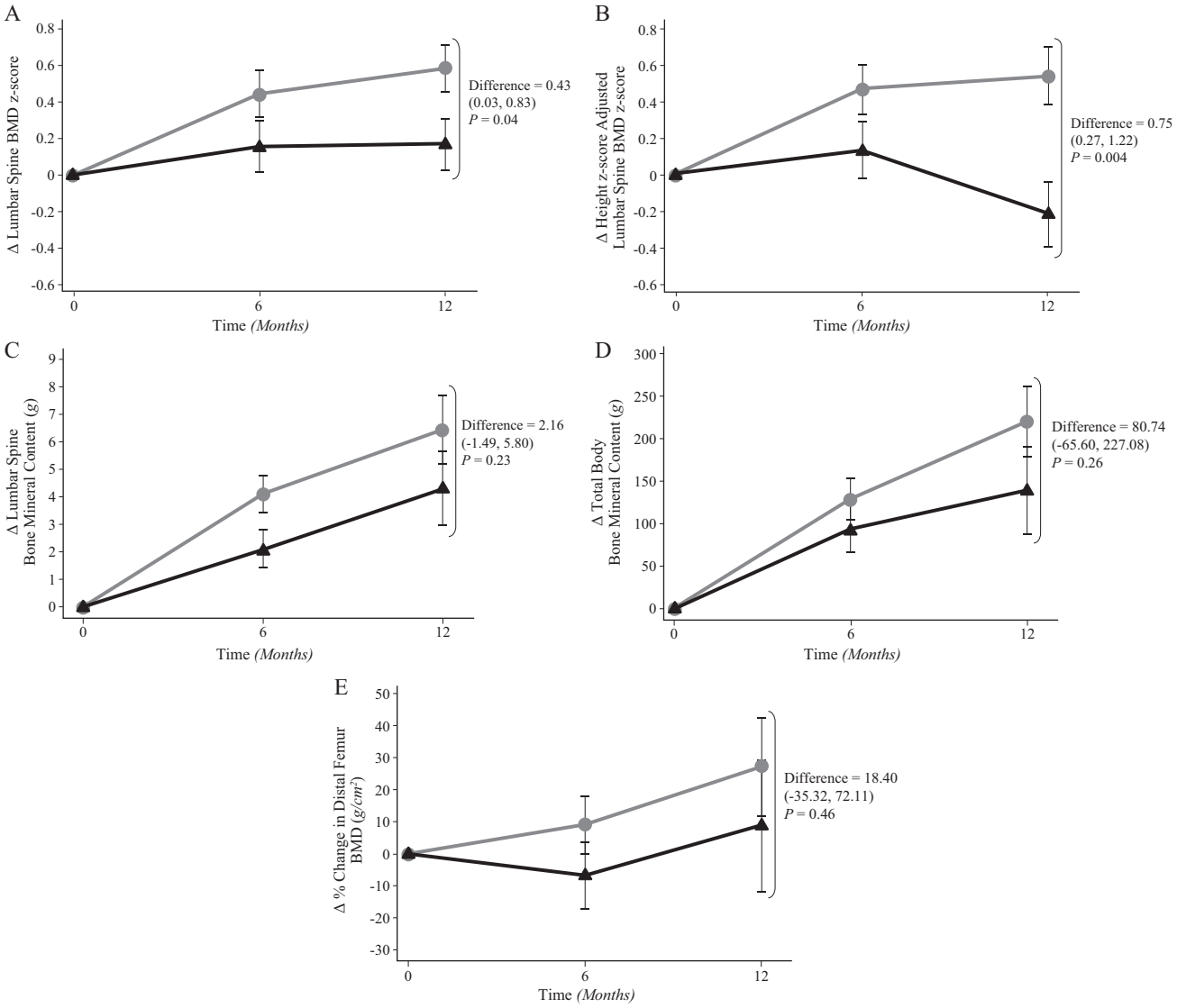

Figure 2. A to E, Changes in bone mass and density from baseline to month 12 in children on zoledronic acid (gray circles) vs placebo (black triangles). N = 17 zoledronic acid, N = 16 placebo. BMD, bone mineral density. Results are expressed as the least squares mean and SE. Differences in the changes are reported, along with their 95% CI.

treatment because of incident fractures as previously described. The incidences of AEs, drug-related AEs, and SAEs were higher in the ZA group (Table 5). Twice as many children on ZA (9/18, 50%) experienced at least one AE that was suspected to be related to the study drug, compared with 25% (4/16) on placebo. Two children had mild (asymptomatic) hypocalcemia following the first dose. One of the patients was prescribed calcitriol because of a history of a seizure disorder, and both cases of asymptomatic hypocalcemia resolved uneventfully. There was one patient in each group who had a single hypophosphatemic event during the course of the study, as measured 10 days after each infusion.

SAEs were observed in 1 patient on placebo (1/16, 6%) who had a varicella zoster infection, and in 4 children (5/18, 28%) on ZA. One child with SAEs and systemic lupus erythematosus was hospitalized the day after the first ZA dose for a ZA-related "acute-phase reaction," including nausea, vomiting, headache, bone pain, and myalgia. Another patient with SAEs was hospitalized for 44 days following the second dose of ZA, with symptoms attributed to a known, underlying central nervous system vasculitis. Three other children with SAEs post-ZA were treated for Crohn disease flare-ups starting 2 and 30 days following the first dose; a third child had a Crohn exacerbation that started the day following the second ZA dose. All SAEs resolved uneventfully. There were no AEs related to anaphylaxis, cardiac arrhythmia, osteonecrosis of the jaw, atypical femur fractures, or delayed fracture healing.

Table 2. Height, vertebral morphometry, and second metacarpal cortical width (in modified intention-to-treat population[a])

	Zoledronic acid (n = 17)	Placebo (n = 16)	*P*
Height, cm			
Mo 6, mean (SD)	151.5 (18.3)	144.6 (17.6)	
Change from baseline to mo 6			
Least squares mean (SE)	1.4 (1.5)	0.4 (1.6)	.6
Difference (95% CI)		1.0 (–3.4 to 5.3)	
Mo 12, mean (SD)	154.1 (16.3)	148.2 (18.0)	
Change from baseline to mo 12			
Least squares mean (SE)	3.2 (1.0)	4.8 (1.1)	.27
Difference (95% CI)		–1.7 (–4.7 to 1.4)	
Height, *z* score			
Mo 6, mean (SD)	–0.7 (1.4)	–1.3 (1.3)	
Change from baseline to mo 6			
Least squares mean (SE)	0.2 (0.2)	0.1 (0.2)	.83
Difference (95% CI)		0.1 (–0.5 to 0.6)	
Mo 12, mean (SD)	–0.4 (1.4)	–0.8 (1.2)	
Change from baseline to mo 12			
Least squares mean (SE)	0.5 (0.2)	0.7 (0.2)	.45
Difference (95% CI)		–0.2 (–0.7 to 0.3)	
Vertebral morphometry (average mid-to-posterior height ratio L1-L4)			
Mo 12, mean (SD)	1.0 (0.0)	1.0 (0.1)	
Change from baseline to mo 12			
Least squares mean (SE)	–0.0 (0.0)	–0.0 (0.0)	.32
Difference (95% CI)		–0.0 (–0.1 to 0.0)	
Second metacarpal cortical width, mm			
Mo 12, mean (SD)	0.4 (0.2)	0.4 (0.1)	
Change from baseline to mo 12			
Least squares mean (SE)	–0.0 (0.0)	0.0 (0.0)	.52
Difference (95% CI)		–0.0 (–0.2 to 0.1)	

Abbreviations: ITT, intention-to-treat; mITT, modified intention-to-treat.
[a]mITT population = all patients in the ITT population who had an evaluable baseline assessment for the end point of interest.

Discussion

In this first randomized, placebo-controlled study of an IV bisphosphonate in children with bone fragility, we have shown greater increases in LS BMD *z* score on ZA compared with IV placebo in children with serious, GC-treated illnesses. Children with GC-treated diseases can develop disabling complications of osteoporosis, including painful VFs in a variety of GC-treated contexts (1, 5), and premature, permanent loss of ambulation following long bone fractures in those with tenuous mobility (5). In contrast to the pediatric osteogenesis imperfecta literature, there have been relatively few studies on the response to IV bisphosphonate therapy in children with GC-treated disorders (26), in part because of the challenges in studying children with heterogeneous underlying diseases, and the lower frequency of fractures compared with primary osteoporotic conditions. Given the lack of placebo-controlled data on IV bisphosphonate therapy in any pediatric population with bone fragility, this study provides important, novel information about the safety and efficacy of ZA in children.

We have shown that GC-treated children with underlying rheumatic conditions, inflammatory bowel disease, and DMD had significant increases in LS BMD *z* score on IV ZA compared with IV placebo. Seventy-four percent of the increase was achieved in the first 6 months of therapy, and the magnitude of the *z* score difference between groups was 0.41 at month 12. It is also noteworthy that the greater increases in LS BMD *z* score occurred even though the ZA group grew on average 3.2 cm over the 12 months, compared with 4.8 cm on placebo. This is an important observation, since linear growth is a key stimulus for bone mineral accrual in childhood (27).

The magnitude of the difference in LS BMD *z* score between the ZA and placebo groups in our study exceeds findings in GC-treated children on oral risedronate compared with placebo, or alfacalcidol, for 1 year (28). In a randomized, placebo-controlled trial by Rooney et al (n = 217, 86% without fractures at baseline), the difference in the LS BMD *z* score change over 1 year was 0.27 ($P < .001$) on risedronate compared with placebo, and 0.33 ($P < .001$) on risedronate compared with alfacalcidol

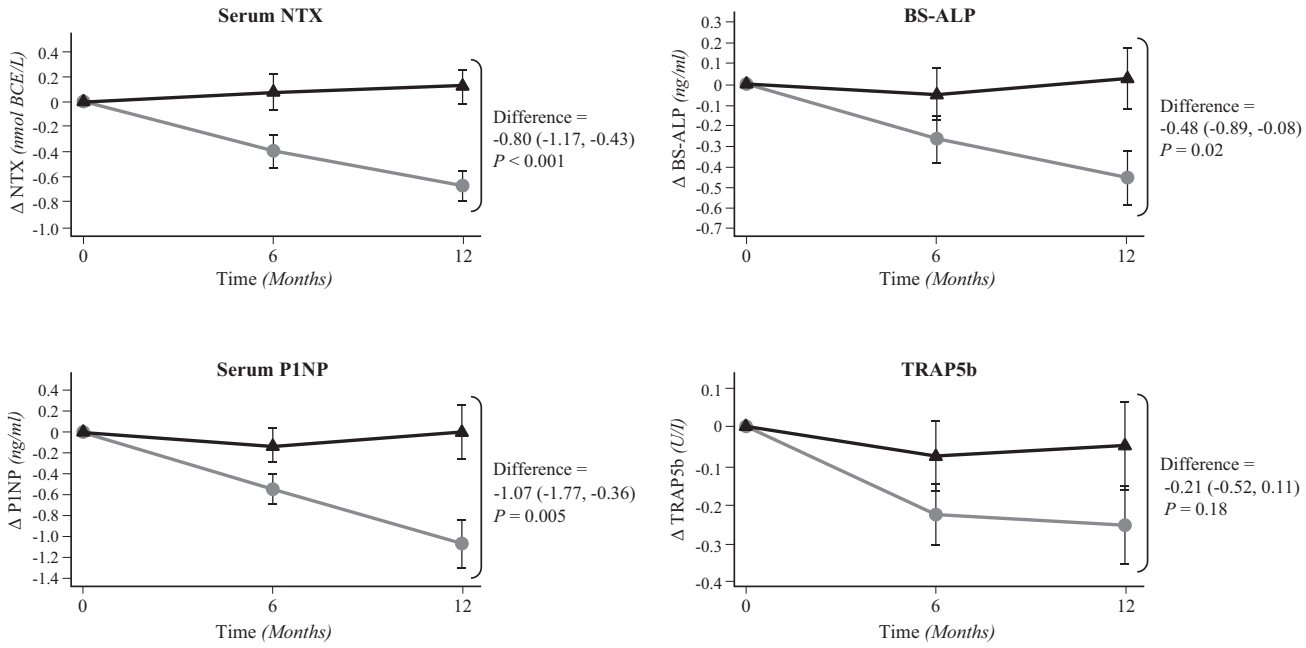

Figure 3. Changes in bone turnover markers baseline to month 12 in children on zoledronic acid (gray circles) vs placebo (black triangles). N = 17 zoledronic acid, N = 16 placebo. BS-ALP, bone-specific alkaline phosphatase; NTX, cross linked N-telopeptide; P1NP, N-terminal propeptide type I collagen; TRAP5b, tartrate-resistant acid phosphatase isoform 5b. Results are expressed as the least squares mean and SE. Differences in the changes are reported, along with their 95% CI.

Table 3. Faces Pain Scale–Revised (in modified intention-to-treat population[a])

Visit	Zoledronic acid (N = 17)	Placebo (N = 16)
Mo 3		
Responder[b], n (%)	6/16 (38)	7/13 (54)
Odds ratio, 95% CI		0.45 (0.04-5.20)
P		.52
Mo 6		
Responder, n (%)	6/16 (38)	7/14 (50)
Odds ratio, 95% CI		>999.9 (< 0.0-> 999.9)
P		.52
Mo 9		
Responder, n (%)	5/15 (33)	6/13 (46)
Odds ratio, 95% CI		0.5 (0.0-6.2)
P		.60
Mo 12		
Responder, n (%)	5/16 (31)	8/14 (57)
Odds ratio, 95% CI		0.45 (< 0.01-> 999.99)
P		.97

Abbreviations: ITT, intention-to-treat; mITT, modified intention-to-treat.

[a]mITT population = all patients in the ITT population who had an evaluable baseline assessment for the end point of interest.

[b]A responder was defined as a child with a decrease in the Faces Pain Scale–Revised from baseline. The odds ratio is the odds of a zoledronic acid treated patient being a responder, relative to the odds of a placebo-treated patient, based on a logistic regression model with treatment, pooled centers, underlying condition, and baseline pain score as explanatory variables. The *P* value of treatment comparison is based on the logistic regression model.

(28). These smaller differences occurred despite changes in height that were similar to those in our study. The magnitude of the increase in LS BMD *z* score on IV ZA in our report, while greater than on oral risedronate (28), was nevertheless smaller than in studies of both oral (29) and IV (30) bisphosphonates in children with osteogenesis imperfecta. One explanation for this difference may be that linear growth is typically associated with increasing areal BMD in childhood; however, in GC-treated children, growth (and by inference BMD accrual) is often blunted by toxic effects of GC therapy on growth plate chondrocytes (31).

Table 4. Exploratory outcomes (in modified intention-to-treat population)

	ZA (n = 17)	Placebo (n = 16)
PedsQL total score[b]		
Child Report	**ZA (n = 6/17)**	**Placebo (n = 9/16)**
Baseline, mean (SD)	37.2 (13.9)	41.4 (12.6)
Mo 12, mean (SD)	27.6 (15.8)	32.8 (15.6)
Mean change from baseline to mo 12 (SD)	−5.0 (13.8)	−8.7 (13.5)
Parent Report	**ZA (n = 8/17)**	**Placebo (n = 9/16)**
Baseline, mean (SD)	43.1 (7.2)	43.3 (19.0)
Mo 12, mean (SD)	35.1 (14.2)	36.2 (14.56)
Mean change from baseline to mo 12 (SD)	−7.7 (11.4)	−7.1 (16.0)
North Star Ambulatory Assessment Total Score[c] **% change (boys with DMD)**		
	ZA (n = 5/5)	**Placebo (n = 6/7)**
Baseline, mean (SD)	6.6 (12.6)	7.2 (7.5)
Median (Q1-Q3)	2.0 (0, 2)	5.5 (0, 15)
Mo 12, mean (SD)	7.3 (13.2)	5.7 (7.9)
Median (Q1-Q3)	1.0 (0 to 14.5)	2.0 (0 to 10)
Mean % change from baseline to mo 12 (SD)	−53.4 (65.8)	−31.0 (37.9)
Median (Q1-Q3)	−53.45 (−100 to −6.9)	−33.33 (−54.2 to −7.8)

Comparisons were not made between the 2 groups for these exploratory outcomes because of considerable missing data for the PedsQL, and small sample size for the North Star Ambulatory Assessment.

Abbreviations: DMD, Duchenne muscular dystrophy; ITT, intention-to-treat; mITT, modified intention-to-treat; PedsQL, Pediatric Quality of Life inventory; ZA, zoledronic acid.

[a]mITT population = all patients in the ITT population who had an evaluable baseline assessment for the end point of interest.

[b]The higher the PedsQL 4.0 score, the lower the child's quality of life. A decline in PedsQL score indicates improved quality of life.

[c]The higher the North Star Ambulatory Assessment total score, the better the boy's functional status. A decrease in North Star Ambulatory Assessment indicates a decline in muscle function.

Fracture rates were low after 1 year in the report by Rooney and colleagues (28), but there was insufficient power to detect statistically significant differences. In that study, all the patients in the risedronate group, and most on placebo (54/77, 70%), did not have VFs at baseline. However, it is noteworthy that 3 children on risedronate had incident VFs at 12 months, including 1 child without VFs at baseline who developed a severe (grade 3) VF at 12 months. This was in contrast to our study, in which no children sustained low-trauma incident VFs in the ZA group, compared with 2 on placebo. Back pain was low in both groups at baseline and throughout our trial, consistent with the frequently asymptomatic nature of VFs in GC-treated children (2).

A striking contrast between our study and that of Rooney et al (28) was that all measured bone turnover markers (BS-ALP, serum cross-linked C-telopeptide of type I collagen [CTX], and osteocalcin) increased on risedronate, whereas in our study serum NTX, PINP, and BS-ALP declined significantly on ZA. Our results are consistent with the significant decline in bone turnover markers observed in the randomized, placebo-controlled pilot study of IV ZA 0.07 mg/kg every 6 months in children with Crohn disease and osteopenia (of whom 30% were GC treated) (9). Since a sustained decline in serum bone turnover markers is the biological signature of antiresorptive therapy even in high bone turnover states (32), our findings are reassuring. The fact that TRAP5b did not decline on ZA in our study is in line with observations in pediatric osteogenesis imperfecta (32), where lack of TRAP5b decline has been hypothesized to result from the persistence of giant, albeit less functional, osteoclasts on IV bisphosphonates (33).

The safety profile of ZA was overall consistent with detailed AE reporting in 2 large, retrospective observational studies of IV bisphosphonate therapy in children with primary and secondary osteoporosis (including 24 to 33% who had GC-treated diseases) (11, 15). Similar to our study, most AEs occurred following the first dose, consistent with the well-known "acute-phase reaction" (11, 15). However, gastrointestinal symptoms were more frequent in our report, occurring in 50% of children on ZA, and in 31% on placebo. In our study, 39% on ZA and 13% on placebo had Crohn disease, which may have contributed to the higher frequency of gastrointestinal side effects overall. In addition, there was a high frequency of AEs on placebo, occurring in 75% of such children, compared with 83% on ZA. The fact that 25% of children on placebo reported AEs within 10 days of the first dose underscores that an

Table 5. Treatment-emergent adverse events (in safety population[a])

Assessment, n (%)	Zoledronic acid (n = 18)	Placebo (n = 16)
AEs	15 (83)	12 (75)
Related AE	9 (50)	4 (25)
Serious AE	5 (28)	1 (6)
Serious related AE	1 (6)	0 (0)
AE of interest		
AE within first 10 d of first dose	12 (67)	4 (25)
AE within first 10 d of second dose	1 (6)	1 (6)
Arthralgia/Myalgia/Bone Pain	6 (33)	2 (13)
Fever	4 (22)	1 (6)
Hypocalcemia	2 (11)	0 (0)
AEs with at least 10% in either group by preferred term		
Cardiac disorders	3 (17)	0
Tachycardia	3 (17)	0
Endocrine disorders	3 (17)	0
Adrenal insufficiency	3 (17)	0
Gastrointestinal disorders	9 (50)	5 (31)
Vomiting	4 (22)	1 (6)
Nausea	3 (17)	2 (13)
Abdominal discomfort	2 (11)	0
Crohn disease	2 (11)	0
Diarrhea	2 (11)	0
General disorders	7 (39)	3 (19)
Pain	3 (17)	0
Acute-phase reaction	2 (11)	0
Fatigue	1 (6)	2 (13)
Infectious illnesses	4 (22)	8 (50)
Upper respiratory tract infection	2 (11)	3 (19)
Herpes zoster	0	2 (13)
Nutrition disorders	2 (11)	2 (13)
Nervous system disorders	4 (22)	1 (6)
Headache	4 (22)	1 (6)

A patient with multiple occurrences of an AE for the same preferred term or system organ class was counted only once in each specific category.
Abbreviations: AE, adverse event; SAE, serious adverse event.
[a]Safety population = all patients who were exposed to at least one infusion of study drug.

underlying disease exacerbation should be considered even when symptoms occur soon after ZA. George et al (15) reported AEs more frequently in children with secondary (42%) compared with primary (14%) osteoporosis, which is not surprising given the myriad symptoms associated with systemic, GC-treated illnesses. In our study, hypocalcemia was infrequent, mild, and asymptomatic on ZA, whereas reports of symptomatic hypocalcemia requiring hospitalization have been observed by others (11, 15). The absence of symptomatic hypocalcemia may have resulted from careful attention to adequate vitamin D and calcium intake in participants prior to and during the trial. Asymptomatic hypophosphatemia was also observed on central laboratory reporting at 10 days post infusion, a finding that has also been reported by others (15, 34).

An important methodological consideration relevant to osteoporosis trials is that LS BMD *z* score, when used as a threshold (binary) variable, is challenging. This is because children with GIO can fracture at BMD *z* scores above –2.0 (2, 35). In our study, the LS BMD *z* score eligibility threshold was set much higher than this (≤ 0.5), and the presence of clinically significant fractures was also required. This ensured that children with LS BMD *z* scores between –2.0 and 0.5 or less were not excluded from participation in the trial (provided they also had overt bone fragility). Another consideration in the use of BMD *z* scores in pediatric clinical trials is that the *z* scores can vary by as much as 2 SD, depending on the normative database used to generate the *z* scores (35). On the other hand, when the LS BMD *z* score is implemented as a continuous variable, there is a consistent relationship between the lower LS BMD *z* score and an increase in the odds of a VF and vice versa, regardless of the normative database chosen to generate the *z* scores (35). As a result, it is anticipated that the greater increase in LS BMD *z* scores observed in the ZA group would decrease the low-trauma VF risk. Although

there was insufficient power to test this outcome, the fact that there were 2 children on placebo with low-trauma VF (one each) and none in the ZA group supports this concept.

With only 37% of the target sample size achieved despite 9 years of recruitment, this study affirms the challenges of osteoporosis drug trials in pediatric GC-treated disorders (36). Two of the specific barriers to enrollment in this trial that we observed were as follows. First, the osteoporosis phenotype of DMD is so aggressive that it was inappropriate at many sites (relative to the standard of care) to enroll boys with DMD and symptomatic VF into a placebo-controlled trial. Second, the use of biologic agents to treat inflammation in lieu of prolonged or even short-term GC therapy appears to have reduced the overall frequency of GIO in children. Apart from recruitment challenges, a limitation of this study was that comprehensive documentation of cumulative GC exposure was not achieved over the 12-month period. All children received at least one dose of GC for the treatment of their underlying disease in the 12 months preceding screening. In addition, 61% of children on ZA went on to receive at least one dose of GC for their disease during the trial, compared with 25% on placebo. While the greater increases in height and bone turnover markers among patients on placebo are consistent with reduced GC exposure in this group, we were unable to verify this unequivocally.

Conclusions

To our knowledge, this is the first randomized, placebo-controlled trial of an IV bisphosphonate in children with bone fragility. We have shown that GC-treated children with VFs receiving IV ZA 0.05 mg/kg every 6 months for 1 year had significant increases in LS BMD *z* scores compared with placebo. Reductions in bone turnover markers were also observed on ZA, in keeping with the expected biological response to antiresorptive therapy. The safety profile was consistent with the previously reported, transient side effects of ZA.

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Data Availability: Novartis is committed to sharing with qualified external researchers, access to patient-level data, and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel based on scientific merit. All provided data are anonymized to respect the privacy of patients who have participated in the trial, in line with applicable laws and regulations. The criteria and process for trial data availability are described online. For trial data availability, see https://www.clinicalstudydatarequest.com/.

References

1. LeBlanc CM, Ma J, Taljaard M, et al; Canadian STeroid-Associated Osteoporosis in Pediatric Population (STOPP) Consortium. Incident vertebral fractures and risk factors in the first three years following glucocorticoid initiation among pediatric patients with rheumatic disorders. *J Bone Miner Res*. 2015;**30**(9):1667-1675.
2. Rodd C, Lang B, Ramsay T, et al; Canadian Steroid-Associated Osteoporosis in the Pediatric Population (STOPP) Consortium. Incident vertebral fractures among children with rheumatic disorders 12 months after glucocorticoid initiation: a national observational study. *Arthritis Care Res (Hoboken)*. 2012;**64**(1):122-131.
3. Ward LM, Ma J, Lang B, et al; Steroid-Associated Osteoporosis in the Pediatric Population (STOPP) Consortium. Bone morbidity and recovery in children with acute lymphoblastic leukemia: results of a six-year prospective cohort study. *J Bone Miner Res*. 2018;**33**(8):1435-1443.

4. Joseph S, Wang C, Bushby K, et al; UK NorthStar Clinical Network. Fractures and linear growth in a nationwide cohort of boys with Duchenne muscular dystrophy with and without glucocorticoid treatment: results from the UK NorthStar database. *JAMA Neurol*. 2019;**76**(6):701-709.
5. Ma J, McMillan HJ, Karagüzel G, et al. The time to and determinants of first fractures in boys with Duchenne muscular dystrophy. *Osteoporos Int*. 2017;**28**(2):597-608.
6. Marrani E, Giani T, Simonini G, Cimaz R. Pediatric osteoporosis: diagnosis and treatment considerations. *Drugs*. 2017;**77**(6):679-695.
7. Inoue Y, Shimojo N, Suzuki S, et al. Efficacy of intravenous alendronate for the treatment of glucocorticoid-induced osteoporosis in children with autoimmune diseases. *Clin Rheumatol*. 2008;**27**(7):909-912.
8. Acott PD, Wong JA, Lang BA, Crocker JF. Pamidronate treatment of pediatric fracture patients on chronic steroid therapy. *Pediatr Nephrol*. 2005;**20**(3):368-373.
9. Sbrocchi AM, Forget S, Laforte D, Azouz EM, Rodd C. Zoledronic acid for the treatment of osteopenia in pediatric Crohn's disease. *Pediatr Int*. 2010;**52**(5):754-761.
10. Ward LM, Konji VN, Ma J. The management of osteoporosis in children. *Osteoporos Int*. 2016;**27**(7):2147-2179.
11. Nasomyont N, Hornung LN, Gordon CM, Wasserman H. Outcomes following intravenous bisphosphonate infusion in pediatric patients: a 7-year retrospective chart review. *Bone*. 2019;**121**:60-67.
12. Simm PJ, Johannesen J, Briody J, et al. Zoledronic acid improves bone mineral density, reduces bone turnover and improves skeletal architecture over 2 years of treatment in children with secondary osteoporosis. *Bone*. 2011;**49**(5):939-943.
13. Ooi HL, Briody J, Biggin A, Cowell CT, Munns CF. Intravenous zoledronic acid given every 6 months in childhood osteoporosis. *Horm Res Paediatr*. 2013;**80**(3):179-184.
14. Sbrocchi AM, Rauch F, Jacob P, et al. The use of intravenous bisphosphonate therapy to treat vertebral fractures due to osteoporosis among boys with Duchenne muscular dystrophy. *Osteoporos Int*. 2012;**23**(11):2703-2711.
15. George S, Weber DR, Kaplan P, Hummel K, Monk HM, Levine MA. Short-term safety of zoledronic acid in young patients with bone disorders: an extensive institutional experience. *J Clin Endocrinol Metab*. 2015;**100**(11):4163-4171.
16. Genant HK, Jergas M, Palermo L, et al. Comparison of semiquantitative visual and quantitative morphometric assessment of prevalent and incident vertebral fractures in osteoporosis The Study of Osteoporotic Fractures Research Group. *J Bone Miner Res*. 1996;**11**(7):984-996.
17. de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. *Bull World Health Organ*. 2007;85(9):660–667.
18. Gauld LM, Kappers J, Carlin JB, Robertson CF. Height prediction from ulna length. *Dev Med Child Neurol*. 2004;**46**(7):475-480.
19. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. *Arch Dis Child*. 1969;**44**(235):291-303.
20. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. *Arch Dis Child*. 1970;**45**(239):13-23.
21. Land C, Rauch F, Munns CF, Sahebjam S, Glorieux FH. Vertebral morphometry in children and adolescents with osteogenesis imperfecta: effect of intravenous pamidronate treatment. *Bone*. 2006;**39**(4):901-906.
22. Hicks CL, von Baeyer CL, Spafford PA, van Korlaar I, Goodenough B. The Faces Pain Scale–Revised: toward a common metric in pediatric pain measurement. *Pain*. 2001;**93**(2):173-183.
23. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. *Med Care*. 2001;**39**(8):800-812.
24. Mercuri E, Coratti G, Messina S, et al. Revised North Star Ambulatory Assessment for young boys with Duchenne muscular dystrophy. *PloS One*. 2016;**11**(8):e0160195.
25. Zemel BS, Kalkwarf HJ, Gilsanz V, et al. Revised reference curves for bone mineral content and areal bone mineral density according to age and sex for black and non-black children: results of the Bone Mineral Density in Childhood Study. *J Clin Endocrinol Metab*. 2011;**96**(10):3160-3169.
26. Jayasena A, Atapattu N, Lekamwasam S. Treatment of glucocorticoid-induced low bone mineral density in children: a systematic review. *Int J Rheum Dis*. 2015;**18**(3):287-293.
27. Rauch F, Bailey DA, Baxter-Jones A, Mirwald R, Faulkner R. The 'muscle-bone unit' during the pubertal growth spurt. *Bone*. 2004;**34**(5):771-775.
28. Rooney M, Bishop N, Davidson J, et al; British Society for Paediatric and Adolescent Rheumatology UK. The prevention and treatment of glucocorticoid-induced osteopaenia in juvenile rheumatic disease: a randomised double-blind controlled trial. *EClinicalMedicine*. 2019;**12**:79-87.
29. Ward LM, Rauch F, Whyte MP, et al. Alendronate for the treatment of pediatric osteogenesis imperfecta: a randomized placebo-controlled study. *J Clin Endocrinol Metab*. 2011;**96**(2):355-364.
30. Rauch F, Plotkin H, Zeitlin L, Glorieux FH. Bone mass, size, and density in children and adolescents with osteogenesis imperfecta: effect of intravenous pamidronate therapy. *J Bone Miner Res*. 2003;**18**(4):610-614.
31. Chrysis D, Ritzen EM, Sävendahl L. Growth retardation induced by dexamethasone is associated with increased apoptosis of the growth plate chondrocytes. *J Endocrinol*. 2003;**176**(3):331-337.
32. Rauch F, Plotkin H, Travers R, Zeitlin L, Glorieux FH. Osteogenesis imperfecta types I, III, and IV: effect of pamidronate therapy on bone and mineral metabolism. *J Clin Endocrinol Metab*. 2003;**88**(3):986-992.
33. Cheung MS, Glorieux FH, Rauch F. Large osteoclasts in pediatric osteogenesis imperfecta patients receiving intravenous pamidronate. *J Bone Miner Res*. 2009;**24**(4):669-674.
34. Högler W, Yap F, Little D, Ambler G, McQuade M, Cowell CT. Short-term safety assessment in the use of intravenous zoledronic acid in children. *J Pediatr*. 2004;**145**(5):701-704.
35. Ma J, Siminoski K, Alos N, et al; Canadian STOPP Consortium. The choice of normative pediatric reference database changes spine bone mineral density Z-scores but not the relationship between bone mineral density and prevalent vertebral fractures. *J Clin Endocrinol Metab*. 2015;**100**(3):1018-1027.
36. Brown JJ, Zacharin MR. Attempted randomized controlled trial of pamidronate versus calcium and calcitriol supplements for management of steroid-induced osteoporosis in children and adolescents. *J Paediatr Child Health*. 2005;**41**(11):580-582.