Isotretinoin (13-cis-retinoic acid) is a treatment for recalcitrant nodular acne with a purported effect on bone mineral density (BMD) in the spine. The side effects of isotretinoin on vertebral bone were evaluated in the current study to assess the safety of a new FDA-approved isotretinoin formulation, Lidoise-isotretinoin (Cip-Iso).

**METHODS**

This double-blind, randomized, Phase III, active control, parallel-group, multicenter study evaluated the safety and efficacy of Cip-Iso compared to a marketed isotretinoin (reference product) in patients with severe recalcitrant nodular acne. To ensure optimum DXA assessments the following subjects were excluded at screening: those with metal prosthetics in the spine, hip, or femur; fewer than 3 evaluable lumbar vertebrae between L1 and L4; or BMD Z-score ≤ -2.0. 357 pediatric male and female patients aged between 12 and 17 years were enrolled (Table 1). Female patients were carefully screened and monitored throughout to avoid pregnancy. Patients underwent 20 weeks of treatment with doses of 0.5-1.0 mg/kg/day and baseline and post-treatment DXA measurements of the PA lumbar spine were obtained utilizing either Hologic or GE (Lunar) scanners. All scans were centrally reviewed and analyzed (BioClinica), ensuring consistency of scanner type per subject and instrumentation calibration monitored. 165 of the 357 subjects had height documented and height adjusted Z-scores (HAZ) for the lumbar spine were calculated.

**RESULTS**

The mean spine Z-Scores on the 184 Cip-Iso subjects and the 173 reference product subjects were not statistically different at baseline (visit 1) and post-treatment (visit 8) (Figure 1A, Table 2). The mean HAZ were not statistically different either (Figure 1B, Table 2). Although the change in Z-score between baseline and post-treatment was statistically significant for both Cip-Iso and the reference product (p < 0.001, p = 0.038, respectively), significant was lost when HAZ for each compound were used (Figure 2).

**CONCLUSION**

Two formulations of isotretinoin do not demonstrate a statistically or clinically significant difference from one another in their effect on spine bone density. All studies demonstrated mean positive baseline Z-scores at study entry, likely due to the exclusion of patients with Z-scores of ≤ -2.0 from the study. The HAZ demonstrated similar results. Both drugs demonstrated a statistically significant, but clinically insignificant, decline in Z-score (Figure 2). When adjusting for height, HAZ, the change during treatment was not significant (p > 0.05). However, when adjusting for DXA manufacturer, only Hologic demonstrated a significant change for Cip-Iso, but not the reference product (Table 3). While the reasons for this are currently unknown, one hypothesis is the beam geometries for the two DXA systems result in different results in growing subjects. For example, Lunar may blur and/or Hologic may accentuate, a change in Z-score in growing subjects. Further analysis of the populations scanned on the two DXA systems may be helpful in testing this hypothesis.

**SUMMARY**

Isotretinoin do not appear to have any clinically meaningful effect on spine BMD in a pediatric population being treated for recalcitrant nodular acne for 6 months.