INTRODUCTION: Hutchinson-Gilford Progeria Syndrome (HGPS) is a rare sporadic autosomal dominant disorder that represents a segmental model of premature aging affecting bone among other tissues. The disease locus for classical HGPS is on a limited region of chromosome 1q, a de novo heterozygous point mutation G608G within exon 11. The gene LMNA normally encodes for the protein lamin A, and in progeria, production of both normal lamin A and the mutant protein, progerin, results. The cellular defects in progeria stem from accumulation of progerin which leads to nuclear membrane distortion and a decreased cellular life span. Bony defects may stem from accumulation of progerin within skeletal tissue. The capacity of a bone to support load depends on its structural properties, which are determined by the material properties of the bone tissue and how that bone tissue is distributed in space. Rigidity is the structural property that governs the ability of a bone to resist axial, bending and torsional loads; it is the integral product of the bone tissue modulus (which is a function of the bone mineral density) and bone cross-sectional geometry. The aim of this study was to evaluate the effect of Progeria on the bone mineral density and structural properties of the appendicular skeleton by comparing the volumetric bone mineral density (vBMD) axial, bending and torsional rigidities measured at the metaphysis and diaphysis of the radius to those of normal, age-matched controls.

METHODS: Twenty-six children, age 3-16 years (15 girls and 11 boys), with classical G608G HGPS (1824 C>T on LMNA met study eligibility and were enrolled. Entry criteria included clinical evidence of Progeria and genetic diagnosis of HGPS (by mutational analysis). To provide normative reference data for the pQCT measures, 60 normal controls were enrolled who were age- and gender-matched to the children with HGPS. Fifty-seven had baseline pQCT data for comparison. The Children’s Hospital Boston Institutional Review Board approved the study protocol. Written informed consent was obtained from the parents of all minors, and study assent from children age 7 years and older. Participants were flown in to this single trial site from 16 different countries and spoke a total of 9 different languages. Consent was provided in written and oral form in the language of origin, and translators were provided during all testing periods for non-English speaking participants. Areal bone mineral density (aBMD) of the total body, total hip (bilateral), and L1-L4 lumbar spine by dual-energy X-ray absorptiometry (DXA, QDR Discovery A, Hologic, Inc., Bedford, MA, USA), were measured at one time point. Measurements were compared with age- and gender-matched controls using pediatric reference software. With this instrument, the average in vivo precision for aBMD (expressed as percent coefficient of variation) for the DXA technologists was 0.62% at the spine and 0.72% at the total hip. A bone age assessment was made for each participant using the Gruelich and Pyle Atlas by one radiologist. Height age calculations were performed by one pediatric endocrinologist (CG). For height-age calculations, we utilized segmental whole body lengths, since joint contractures inherent to HGPS can underestimate true height. Adjusted BMD Z-scores were then generated for those patients whose height and/or bone age was one year or more discrepant from the chronological age, and whose age was above 3 or 4 years, as normative data were available for DXA for age 3 years and above for the spine, and age 4 years and above for the hip. Peripheral quantitative computed tomography (pQCT) bone measures of the left radius were obtained at the 4%, 20%, 50%, and 66% sites using a Stratec XCT 3000 device with a 12-detector unit, voxel size of 0.4 mm, slice thickness of 2.3 mm and scan speed of 25 mm/second (Stratec AG, Birkenfeld, Germany). A scout view was obtained to place the reference line at the 4% site of the radius, adjacent to the growth plate, and measurements were obtained at the 4 specified percentages of radial length proximal to the reference line. Scans were analyzed using Stratec software, version 5.50. The assessment sites were chosen given that a pattern of irregular demineralization noted by Gordon et al. in a previous study of HGPS. The axial, bending and torsional rigidities (Figure 1) for each transaxial cross-sectional image through the bone containing were calculated by summing the modulus-weighted area of each pixel comprising the bone section by its position relative to the centroid of the bone, using a previously established technique called Computed Tomography-based Rigidity Analysis (CTRA).

RESULTS: Bone mineral density was essentially normal in the patients with Progeria and minimally affected by treatment. However, even after correcting for differences in BMI, the axial rigidity of the radius at the metaphysis and diaphysis was 27% less, and the bending and torsional rigidities were 55% less than age-matched, normal controls. The CTRA was able to demonstrate a profound effect over time on the structural properties of the radius: there was ~35% increase in the axial rigidity at the metaphysis and ~70% increase in the bending and torsional rigidities at the metaphysis and diaphysis of Progeria patients two years after treatment.

DISCUSSION: We employed a CT based method to calculate the cross-sectional axial, bending and torsional rigidities of bone in health and disease. Peripheral quantitative computed tomography (pQCT) was performed at serial cross-sections through the radius reflecting the structural properties of the metaphysis, meta- and diaphysis. Progeria appears to affect the structural geometry of the appendicular skeleton to a greater extent than bone mineral density. The pQCT measures of bone density, strength and torsional rigidity afforded insights into the appendicular skeleton, in addition to standard measures of the axial skeleton (as provided by DXA). Further study will be needed to determine if some of the differences noted among these measurements reflect differences in appendicular vs. the axial skeleton in HGPS.