Dr. Elizabeth Shane

Osteoporosis that affects young, otherwise healthy women with intact gonadal function and no secondary cause of bone loss (idiopathic osteoporosis or IOP) is uncommon with an estimated prevalence in the United States of <200,000, based on fragility fractures or low bone mineral density (BMD). Our prior work defined abnormal skeletal microstructure in premenopausal IOP: thin, porous cortices, fewer, thinner, disconnected trabeculae, and reduced stiffness or strength. There is no FDA-approved therapy for premenopausal women with IOP, many of whom have multiple fractures or extremely low BMD. We are currently enrolling 41 premenopausal women with IOP into a randomized, 24-month, two-site, FDA Orphan Diseases Program-funded trial "A Phase 2 Study of Teriparatide for the Treatment of Idiopathic Osteoporosis in Premenopausal Women" (FD003902; PI, Shane). We hypothesize that teriparatide (TPTD), which increases bone formation, will increase areal and volumetric BMD, restore abnormal microarchitecture towards normal, and increase bone strength in premenopausal IOP. However, emerging data from an earlier, open-label pilot study of TPTD in premenopausal IOP indicates that TPTD-associated gains in BMD begin to dissipate by 18-24 months after completion. Thus, we believe FD003902 participants will require antiresorptive therapy after completing TPTD to maintain improvements in bone density and quality. Denosumab (Prolia®) is a fully human monoclonal antibody to receptor activator of nuclear factor-κβ ligand (RANKL) that inhibits development and activity of osteoclasts, decreases bone resorption, increases BMD and lowers fracture rates. It is FDA-approved for postmenopausal and male osteoporosis. We hypothesize that denosumab, initiated after completing two years of TPTD, will maintain or improve areal and volumetric BMD, microstructure and stiffness of the central and peripheral skeleton in premenopausal women with IOP. We will test this hypothesis in a 24-month study of denosumab (60mg SC every 6 months). The 41 subjects participating in FD003902 will not provide sufficient power for a randomized trial. Thus we propose an open-label, Phase IIB study to estimate effects of denosumab on BMD, microstructure and stiffness, which will provide preliminary data to design a future randomized study. The Specific Aims are to estimate effects of denosumab on Aim 1) Areal BMD by DXA of the spine, hip, forearm; Aim 2) Total and trabecular volumetric BMD and stiffness of the spine by central QCT and finite element analysis (FEA); Aim 3) Total, cortical and trabecular volumetric BMD, trabecular microarchitecture, cortical porosity and stiffness of the distal radius and tibia by high resolution peripheral QCT (HR-pQCT) and FEA; and Aim 4) Serum PTH and bone turnover markers and associations between these variables and effects of denosumab on BMD, microarchitecture and stiffness. By investigating therapy for and improving the health of young women with IOP, this proposal addresses a key goal of the Office of Orphan Product Development grant program: to support clinical development of products for rare diseases/conditions where no current therapy exists.