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FOUR-YEAR RESULTS OF A PHASE 2 STUDY OF THE CATHEPSIN K INHIBITOR ODANACATIB IN POSTMENOPAUSAL WOMEN WITH LOW BONE MINERAL DENSITY: EFFECTS ON BONE MINERAL DENSITY AND BONE TURNOVER MARKERS

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Aim: Cathepsin K (CatK) is the primary collagenase in osteoclasts. In a 2-year phase 2 study and its 1-year extension, the selective cathepsin K inhibitor odanacatib (ODN) reduced bone resorption markers and progressively increased bone mineral density (BMD). The study was extended for 2 additional years to further assess ODN efficacy and long-term safety.

Methods: Postmenopausal women with BMD T-scores between -2.0 and -3.5 at the lumbar spine, femoral neck, trochanter or total hip received placebo or ODN at 3, 10, 25 or 50 mg weekly during the 2-year study. In Year 3, participants were re-randomized to ODN 50 mg weekly or placebo. In Years 4/5, women who received placebo or 3 mg ODN in Years 1/2 and placebo in Year 3 were switched to 50 mg ODN for Years 4/5; all others continued with their Year 3 regimen. 141 women entered the extension, and 133 completed 4 years. Endpoints were BMD at the lumbar spine (primary), total hip and hip subregions, and 1/3 radius; levels of biochemical bone turnover markers; and assessments of safety.

Results: During year 4, 100 women received 50 mg ODN and 41 received placebo. Continuous treatment with 50 mg ODN for 4 years induced significant BMD increases from baseline at the spine (10.7%), total hip (8.3%), femoral neck (8.9%), and trochanter (10.3%) and maintained BMD (-0.1%) at the 1/3 radius; BMD changes from Year 3 were 2.8% (spine), 2.5% (total hip), 3.9% (femoral neck), and 2.9% (trochanter). Serum CTx remained low at Year 4 (-41%), whereas BSAP was relatively unchanged (-2%) from baseline. Women who received active treatment for 2 years and switched to placebo for 2 years experienced bone loss, with BMD near baseline for most sites and decreased by 4.5% at the 1/3 radius at the end of Year 4. Levels of bone turnover markers in women who discontinued active treatment after 2 years rose in the first month off-treatment, but all levels returned to baseline by the end of Year 4. ODN was generally well tolerated.

Conclusions: 4 years of ODN treatment increased lumbar spine and hip BMD and was generally well-tolerated in postmenopausal women with low bone mass. Bone formation markers remained relatively unaffected. Discontinuation of ODN after 2 years of treatment was promptly followed by resolution of effects on bone turnover and density such that BMD and bone biomarker levels at Year 4 were at or near baseline.

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DXA BODY SCAN DATA FROM NHANES III: "BARREL" BODY FAT DISTRIBUTION PREDICTS CARDIOVASCULAR MORTALITY AND SARCOPENIA PREDICTS NON-CARDIOVASCULAR MORTALITY

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We previously defined DXA derived Barrel body fat distribution as Z-score % trunk fat/total fat (Z-%TF) $>$ 0 and Z-score limb fat/height2 (Z-LF) $<$ 0 and found it to be predictive of 10-year cardiovascular mortality and that sarcopenia defined as Z-score limb lean/height2 (Z-LL) $<$ 0 predicted total mortality. (Preventive Cardiology, 2004;7:109-115) With the recent on-line availability of linked mortality data we examined these ''Mesenchymal Risk'' (MR) associations for the NHANES III DXA data.

Methods: All data were downloaded from public access files (cdc.gov/nchs). Z-scores were computed from DXA scan data by gender, ethnicity (white, Mexican, black) and for age $>$ 18 years, by decade. Cardiovascular (CV) and non- CV mortality were determined by cause of death ICD codes. Odds ratios for mortality were derived for MR with online statistics (faculty.vassar.edu/lowry). Cox proportional hazard modeling (www.r-project.org) for mortality was performed for age, gender, BMI, waist circumference (wc), sarcopenia (Z-LL) and barrel projection (BP = Z-%TF − Z-LF).

Results: Mortality (as of 2006) for NHANES 1999-2000 (5161 subjects) was 10.6%, Odds ratios displayed in Table were significant, with the exception of sarcopenia in Blacks and Barrel in Mexicans. Cox modeling showed that CV mortality increased 24% per unit BP and non-CV mortality increased by 21 % per unit decrease in Z-LL. Conversely, CV mortality was not predicted by Z-LL, neither was non-CV mortality predicted by BP. As single variables CV-mortality was significantly associated only with BP ($p = .013$) but not with wc. Gender differences in mortality were entirely accounted for by MR in these models. Also we found notable that total mortality decreased by 10% for each unit increase in BMI, with a 3% higher risk for each centimeter increase in wc. In analysis of the full NHANES III cohort (14,479 subjects) for each unit decrease Z-LL, mortality increased 14%, but the increased CV mortality for BP was seen only for subjects followed for at least 4 years.

Conclusions: The NHANES III data base confirms that DXA derived MR predicted mortality, with CV-mortality associated with BP and non-CV mortality with sarcopenia. Higher BMI was paradoxically associated with lower mortality while wc was a weaker predictor of CV-mortality than BP. Our results support further consideration of DXA derived MR for individual risk prediction, targeting interventions and design of clinical trials.

Table
NHANES III Mortality Data:

	# Subjects	Deaths CV	Deaths non CV	Sarcopenia Odds ratio non CV (95% CI)	Barrel vs non-Barrel Odds ratio CV (95% CI)
Combined	5161	119	433	1.39113-171	1.741.19-2.53
White non-Hispanic	1926	61	167	1.631.17-2.28	1.811.06-3.07
Black non-Hispanic	906	24	60	1.10.65-1.88	2.611.14-5.96
Mexican	1341	28	66	1.721.02-2.91	1.400.62-3.12

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ACCURACY AND PRECISION OF THE HOLOGIC REFLECTION TECHNIQUE FOR OBESE WHOLE BODY SCAN ANALYSIS

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Background: Due to the increase in obesity and the associated health problems, the ability to scan patients 300 pounds and over has become a very useful capability for DXA systems. However, the size of the scanner tables is limited and in many cases not wide enough to include the full width of the patient. A technique called 'Reflection' is being used by Hologic to estimate whole body values even when an arm or leg falls outside the scan window. The subject is positioned off center so one side of the body is complete. Data from the complete side is ''reflected'' to the incomplete side. We asked what affect the use of this technique has on precision and accuracy.

Methods: Four hundred and thirty four subjects from the NHANES study with repeat whole body scans were chosen, ranging in age from 16 to 69 years. Scans were acquired on Hologic QDR-4500A systems. To mimic ''reflection'' analysis, right arm measures were substituted for the left. Linear regression and Bland-Altman analysis was used to compare the reflected versus whole body scan versions. Precision was estimated as either RMSE and RMS-CV.

Results: Right arm BMD was 3.4% higher than left arm BMD with no significant differences found in the total percent fat. A significant but small difference (250 g) was found for total mass. Small significant differences were observed for whole body bone but no differences on the soft tissue measures. In addition, there was no significant difference in the precision values for any of the variables. The highest RMSE being in the total fat (1.85) and the lowest in total mass (1.06).

Conclusion: Reflected arm values on whole body scans have no impact on whole body precision. However, there may be an impact on the accuracy of bone measures.