

Title: Population PK/PD Modeling of Lumbar Spine Bone Mineral Density Response to 12 Months of Treatment with the Cathepsin K Inhibitor, Odanacatib, and Simulations to Further Evaluate the Dose-Response Relationship

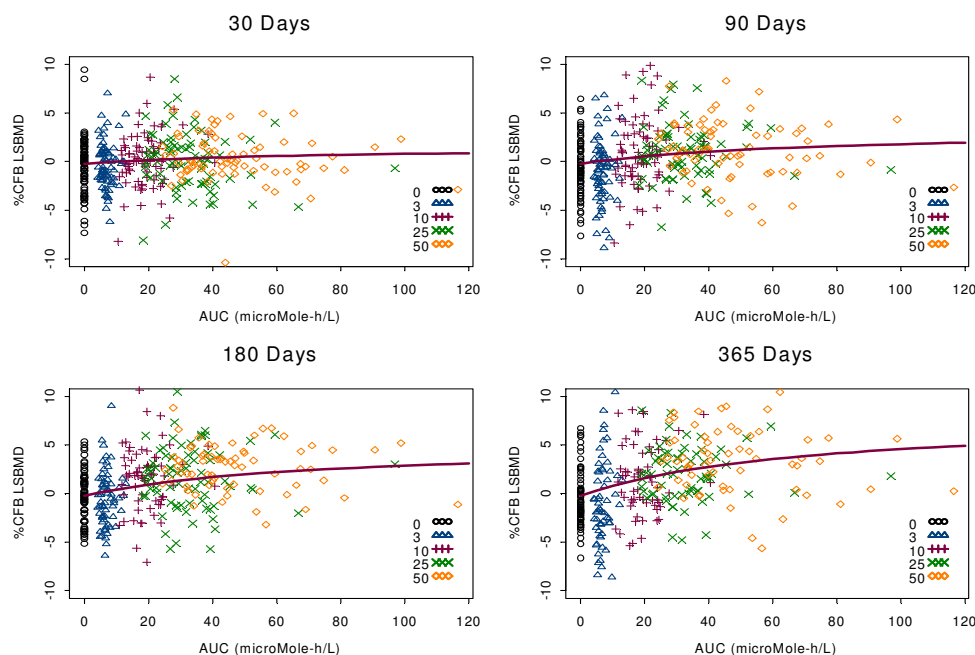
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Objectives: Cathepsin K, a cysteine protease abundantly expressed in osteoclasts, is necessary for bone collagen degradation. Odanacatib, a selective inhibitor of cathepsin K, has been shown to rapidly and reversibly decrease bone resorption and is in development for the treatment of osteoporosis. A Phase II dose-ranging study in 399 women with osteoporosis is ongoing and data out to 12 months were available for modeling [1]. The objectives of this work were to develop a population pharmacokinetic (PK) and pharmacokinetic/pharmacodynamic (PK/PD) model of lumbar spine bone mineral density (lsBMD) and to use these models to further characterize the exposure-response relationship.

Methods: Sparsely sampled PK data out to 6-months and lsBMD PD data out to 12-months were obtained from a Phase IIB study of the safety, tolerability and efficacy of weekly doses of placebo, 3, 10, 25 or 50 mg of odanacatib on BMD and biochemical indices of bone turnover in postmenopausal women with low BMD. Additional PK data for modeling were obtained from a 3 week Phase Ib study in healthy postmenopausal women. The population PK model consisted of a 1-compartment, saturable (dose-dependent bioavailability) absorption PK model and covariates were included to potentially account for differences in the drug lot used in differing study arms and for potential differences between healthy women and osteoporosis patients. Intersubject variability was accounted for in the volume of distribution and elimination rate constant terms. The BMD PK/PD model consisted of a power model $[(\text{time})^Y]$ to represent the time effects, with a simple Emax relationship with area under concentration time curve at steady-state (AUC) to represent drug effects. Intersubject variability was accounted for in the baseline term and a placebo effect was incorporated. The Population PK model was developed in NONMEM V and the BMD PK/PD model was developed in S-Plus. Simulations were conducted and analyzed using Drug Model Explorer (DMX®) and Trial Simulator software.

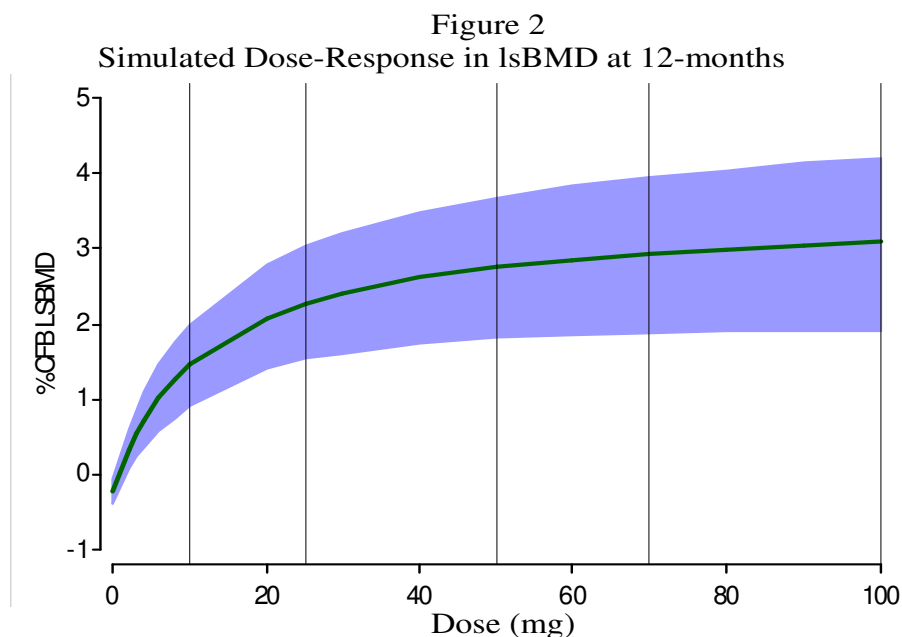
Figure 1
Population Mean PK/PD Model Fit and Observed Data vs Time



Results: The plasma PK data were well represented by the population PK model and individual model predicted steady-state exposure estimates for AUC and C_{trough} were obtained. The relationship between individual lsBMD (% change from baseline) and average steady-state exposure (AUC) in the individual was modeled. The PK measures, C_{max} and C_{trough}, were also investigated, but presented no advantage over AUC. The power model $[(\text{time})^Y]$ used to

represent the time effects, had the fit value ($y=0.62$), since this was <1 this represents a rate of response which is slowing with time. The AUC50 (AUC at which 50% of maximal response is achieved) was estimated as 70 uM.hr. In addition, a modest placebo effect (-0.2%) for BMD decline in the absence of drug was obtained in the model fit. A comparison of the best-line fit of the PK/PD data against the individual data is provided in Figure 1.

The dose-response relationship for 12-month lsBMD response was simulated in DMX and is shown in Figure 2. The simulation results indicate that the 50 mg dose will likely provide greater BMD efficacy than the 25 mg dose. In further support of a conclusion of reduced efficacy at 25 mg, a sensitivity analysis of the AUC50 parameter



indicated that AUC50 value below 40 uM.hr were unlikely. Further simulations of BMD dose-response for doses >50 mg, but ≤ 100 mg, suggested only very modest gains in pushing to higher doses. A trial simulation of a 500 repeat Phase IIB studies, which included an extra 100 mg arm, suggested that a statistically significant improvement in lsBMD would only be obtained in $\sim 14\%$ of trials.

Conclusions: 1) Odanacatib pharmacokinetics in postmenopausal women are well described by a 1-compartment linear model with saturable absorption; 2) Lumbar spine BMD response over 12 months is well described by a power model with time and a simple E_{max} drug effect; 3) Model-based simulation suggest that doses greater than 50 mg weekly provide only slight increase in BMD efficacy and that doses less than 50 mg are likely associated with more meaningful reductions in efficacy.

References:

[1] H. G. Bone¹, M. McClung, N. Verbruggen, A. Rybak-Feiglin, C. DaSilva, A. C. Santora, A. Ince. A Randomized, Double-Blind, Placebo-Controlled Study of a Cathepsin-K Inhibitor in the Treatment of Postmenopausal Women with Low BMD: One Year Results. Oral presentation at ASBMR (September 18, 2007).