Semi-mechanistic PK/PD Model of the Effect of Odanacatib, a Cathepsin K Inhibitor, on Bone Turnover to Characterize Lumbar Spine and Distal Forearm Bone Mineral Density in a Phase IIb Study of Postmenopausal Women

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Background and Objective

Odanacatib (MK-0822), a potent, orally-active inhibitor of cathepsin K, is under clinical development for treatment of postmenopausal osteoporosis. This poster describes base model development of a semi-mechanistic model of bone turnover to describe creatinine adjusted urinary aminoterminal crosslinked telopeptides of Type I collagen (uNTx), a bone resorption biomarker, and lumbar spine and distal forearm bone mineral density (LS- and DF-BMD) data from a Phase IIb dose-ranging study during and after treatment with odanacatib.

Study Design and Results

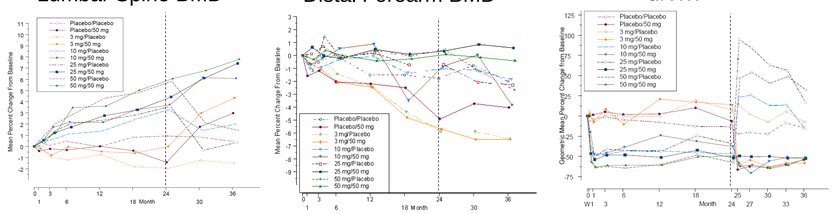
Data from 391 postmenopausal women receiving placebo, 3, 10, 25, or 50 mg weekly odanacatib for up to 2 years (PN004) were utilized. Patients who completed 2 years of treatment were re-randomized to placebo or 50 mg weekly odanacatib and followed for an additional year, providing resolution of effect data in a subset of patients. Odanacatib concentration, biomarker, and LS- and DF-BMD data were collected periodically.

Figure 1 illustrates the mean results for LS-BMD, DF-BMD and uNTx. Several features were of interest with respect to development of a PK/PD model, including:

- Sustained suppression of uNTx and increased LS-BMD throughout 3 year treatment at higher doses
- Elevated uNTx after cessation of treatment and associated LS-BMD changes
- Non-monotonic dose-response relationship for uNTx, LS-BMD and DF-BMD, as the very low dose (3 mg) tended to have slightly enhanced uNTx, slightly reduced LS-BMD and markedly reduced DF-BMD relative to placebo at later treatment timepoints
- Qualitatively different response at distal forearm site compared to lumbar spine

Figure 1: Mean Results from Phase IIb Dose-Ranging Study

Lumbar Spine BMD | Distal Forearm BMD | uNTx



Note: Treatment switch occurred at 24 months (vertical dashed line)

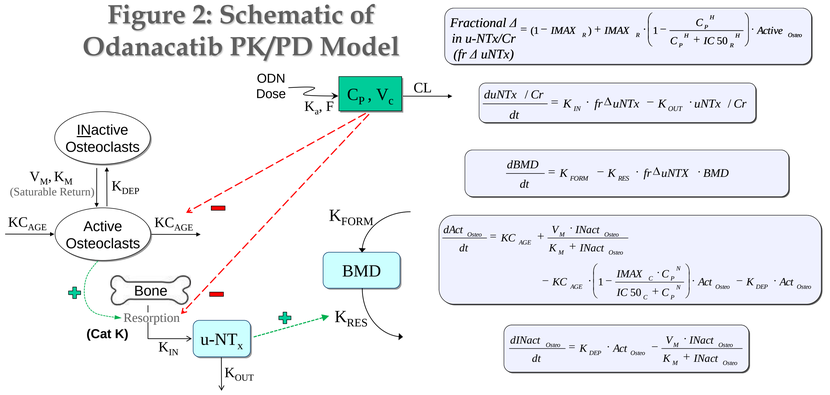
Semi-mechanistic PK/PD Model

A population PK model (1-compartment, linear elimination, saturable bioavailability with dose) was used to estimate individual exposures (concentration-time profiles). An indirect response model characterizes the timecourse of DF- and LS-BMD as functions of bone formation (K_{form}) and resorption (K_{res}) rates, with the uNTx biomarker described as a function of the bone resorption rate process only (Figure 1). K_{form} and K_{res} were determined independently for the distal forearm and lumbar spine sites.

The PK/PD model characterizes the mechanism of action of odanacatib through an inhibitory sigmoid E_{max} function applied to both the bone resorption rate and the release rate of uNTx which is a function of resorption. Transiently elevated bone resorption biomarkers after cessation of treatment is described by incorporating active and inactive osteoclast numbers as system variables and including an osteoclast turnover component with an inhibitory sigmoid E_{max} function describing odanacatib inhibition of osteoclast apoptosis rate to reflect an increase in osteoclast numbers during therapy. Results from preclinical rhesus monkey studies indicate that odanacatib treatment can lead to increased numbers of mature osteoclasts and were the basis for including this element in the model.

Semi-mechanistic PK/PD Model (cont)

Figure 2: Schematic of Odanacatib PK/PD Model



$$\text{Fractional } \Delta \text{ in u-NTx/Cr (fr } \Delta \text{ uNTx)} = (1 - IMAX_R) + IMAX_R \cdot \left(1 - \frac{C_P^H}{C_P^H + IC50_R^H}\right) \cdot Active_{Osteo}$$

$$\frac{duNTx/Cr}{dt} = K_{IN} \cdot fr\Delta uNTx - K_{OUT} \cdot uNTx/Cr$$

$$\frac{dBMD}{dt} = K_{FORM} - K_{RES} \cdot fr\Delta uNTX \cdot BMD$$

$$\frac{dAct_{Osteo}}{dt} = KC_{AGE} + \frac{V_M \cdot INact_{Osteo}}{K_M + INact_{Osteo}} - KC_{AGE} \cdot \left(1 - \frac{IMAX_C \cdot C_P^N}{IC50_C^N + C_P^N}\right) \cdot Act_{Osteo} - K_{DEP} \cdot Act_{Osteo}$$

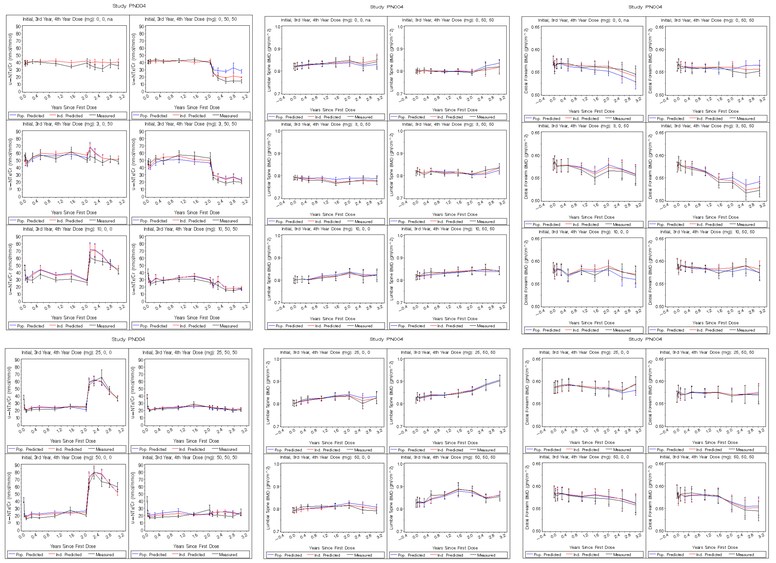
$$\frac{dINact_{Osteo}}{dt} = K_{DEP} \cdot Act_{Osteo} - \frac{V_M \cdot INact_{Osteo}}{K_M + INact_{Osteo}}$$

Bone formation biomarker data were not utilized in parameter estimation, as available data indicate that these biomarkers are not quantitatively predictive of underlying bone formation rate for this therapeutic class. This model assumes that there is no drug effect on bone formation within this range of doses, and thus that effects on BMD can be explained entirely by changes in resorption and osteoclast number.

Results

Population PK/PD modeling was performed using NONMEM with the model simultaneously fit to both uNTx, LS- and DF-BMD data from all treatments. Goodness of fit diagnostics (not shown) and mean overlay plots of PRED, IPRED and observed data (Fig. 4, 5 & 6) indicate that the model characterizes the uNTx, LS and DF-BMD data well.

Figure 4: uNTx | Figure 5: LS-BMD | Figure 6: DF-BMD

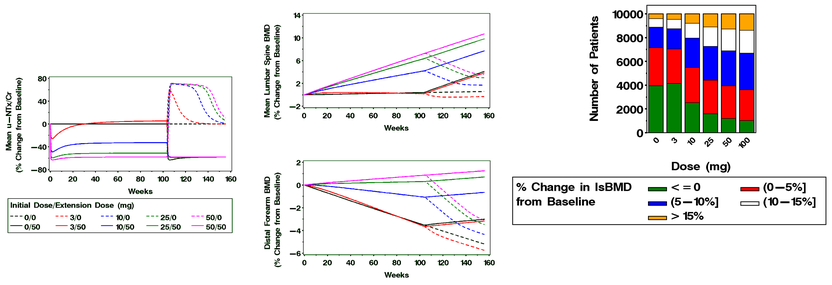


Discussion and Future Directions

Odanacatib Effects on Bone Resorption and BMD

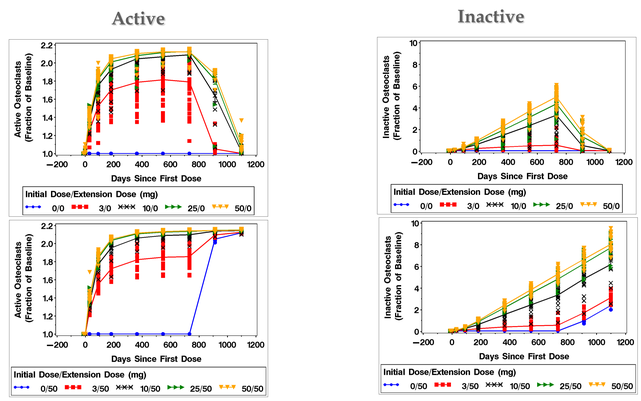
Current model captures the uNTx, LS-BMD and DF-BMD behaviors seen with placebo and the range of odanacatib doses, include both during and post therapy.

Model-Predicted Response for Typical Patients



Only underlying bone formation and resorption rate parameters need to be adjusted between bone sites with primarily cortical (DF-BMD) versus trabecular (LS-BMD) bone. The current model results suggest that within this range of doses, capturing drug effect on resorption and osteoclast number in large part explains the overall BMD response at multiple measurement sites, supporting the idea that resorption and formation are decoupled under Cat-K inhibition. Further work to explore formation effects is ongoing.

Figure 6: Mean Predicted Active and Inactive Osteoclast Response Over Time, Stratified by Treatment Group



At all doses, model predicts accumulation of active and inactive osteoclasts.

3 mg dose leads to elevated osteoclasts, but incomplete resorption inhibition, resulting in non-monotonic dose-response relationship.

Conclusion

- The model supports that a combination of drug effects on bone resorption (E_{max} 70.4%, EC_{50} 41.7 nM) and osteoclast cycling (E_{max} 74.3%, EC_{50} 19.3 nM) can generate the range of behaviors observed in the Phase II data, including a non-monotonic dose-response relationship and enhanced bone resorption post cessation of therapy in both cortical and trabecular bone.
- The model suggests that odanacatib has at most a minor effect on formation at the doses / concentrations tested in this Phase IIb study.