Semi-mechanistic PK/PD Model of the Effect of Odanacatib, a Cathepsin K Inhibitor, on Bone Turnover to Characterize Lumbar Spine Bone Mineral Density in Two Phase II Studies 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 bone mineral density (LS-BMD) data from two Phase II dose-ranging studies during and after treatment with odanacatib.

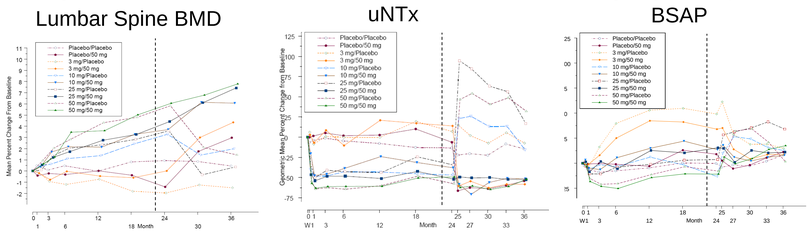
Study Design and Results

Data from 391 postmenopausal women receiving placebo, 3, 10, 25, or 50 mg weekly odanacatib for up to 2 years in PN004 and 266 Japanese postmenopausal women receiving placebo, 10, 25, or 50 mg weekly odanacatib for 1 year in PN022 were utilized. In the first study, 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 BMD data were collected periodically.

Figure 1 illustrates the mean results from the first study for LS-BMD, uNTx, and bone-specific alkaline phosphatase (BSAP), a bone formation biomarker. Several features were of interest to describe with the PK/PD model, including:

- Sustained suppression of uNTx and increased LS-BMD throughout 3 year treatment at higher doses
- Enhanced uNTx after cessation of treatment and associated LS-BMD changes
- Non-monotonic dose-response relationship for uNTx and LS-BMD, as the very low dose (3 mg) tended to have slightly enhanced uNTx and slightly reduced LS-BMD relative to placebo at later treatment timepoints

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



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

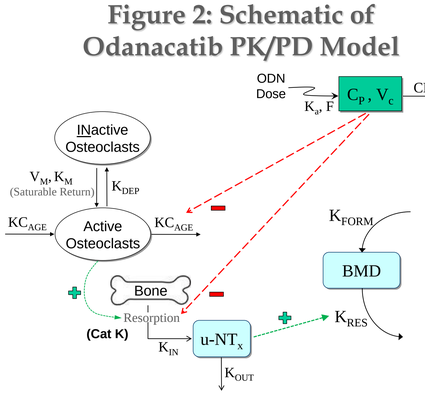
Semi-mechanistic PK/PD Model

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 LS-BMD as a function of bone formation and resorption rate, with the uNTx biomarker described as a function of the bone resorption rate process only (Figure 1).

The PK/PD model characterizes the mechanism of action of odanacatib through an inhibitory sigmoid Emax 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 Emax 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 was the basis for including this element in the model.

Semi-mechanistic PK/PD Model (cont)

Figure 2: Schematic of Odanacatib PK/PD Model



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

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

$$\frac{dBMD}{dt} = K_{FORM} \cdot \left(1 - \frac{TD_{MAX} \cdot Time}{T_{50} + Time}\right) - K_{RES} \cdot fr^{\Delta}uNTx \cdot BMD$$

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

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

A modest decrease in bone formation on treatment with odanacatib was included using an empirical, time-dependent term (hill function with time) to better account for the shape of the BMD response in the first year of treatment; however, bone formation biomarker data was 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.

Results

Population PK/PD modeling was performed using NONMEM with the model simultaneously fit to both uNTx and LS-BMD data from all treatments. Goodness of fit diagnostics (Fig 3.) and visual predictive checks (Fig 4. & 5.) indicate that the model well characterizes the uNTx and LS-BMD data.

Figure 3: Goodness of Fit Diagnostics

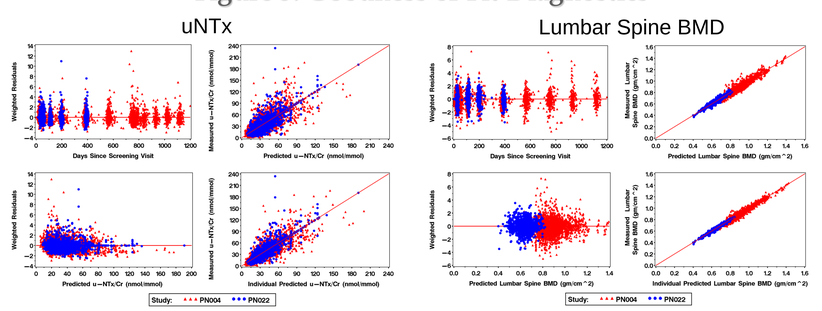
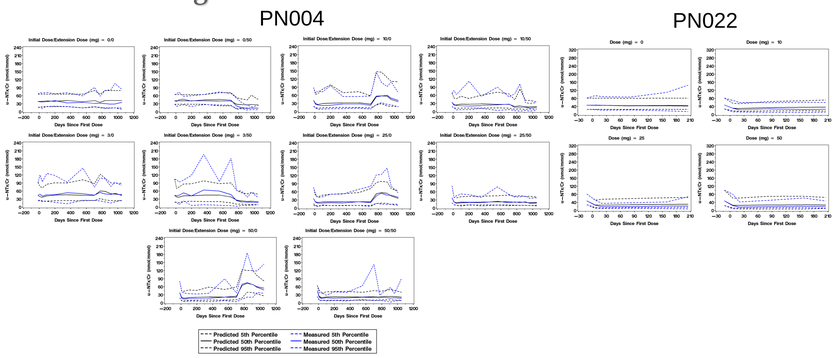
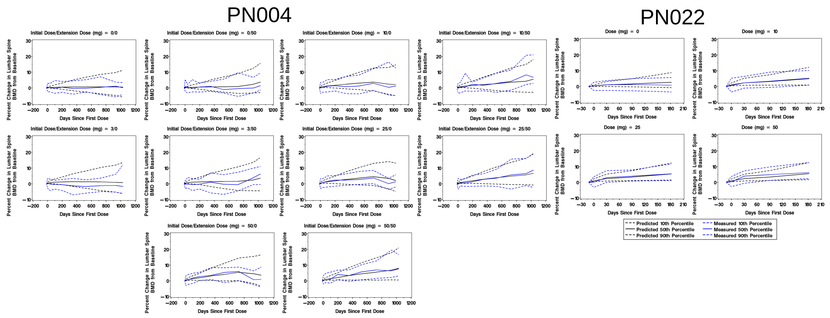


Figure 4: Visual Predictive Check of uNTx



Results (cont.)

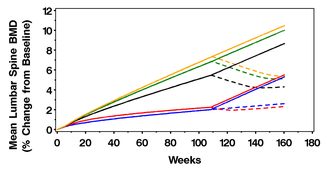
Figure 5: Visual Predictive Check of LS-BMD



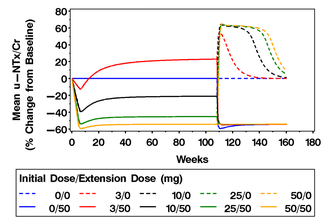
Discussion and Future Direction

Odanacatib Effects on Bone Resorption and BMD

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



Model-Predicted Response for Typical Patients



Odanacatib Effects on Bone Formation

Empirical time-dependent term for effects on formation rates evaluated two ways: applied only to active treated patients or applied to all patients

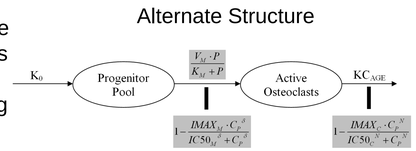
- Estimates when applied to active Tx only: TDMAX=0.159, T50=91.5 days
- Estimates when globally applied: TDMAX=0.637, T50=9.72 days

Effect applied to all patients provided improved fit and suggests that alterations more likely due to non-odanacatib effects, such as supplemental calcium and vitamin D provided to all patients. Further work to explore formation effects are planned.

Odanacatib Effects on Osteoclast Cycling

The current model structure including active and inactive osteoclast pools well describes the data. An alternate structure for the osteoclast cycling component is undergoing evaluation and also appears to reproduce the general behaviors.

Alternate Structure



Conclusion

- The model supports that a combination of drug effects on bone resorption (Emax 67.9%, EC50 38.1 nM) and osteoclast cycling (Emax 72.0%, EC50 17.9 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.
- The model also suggests that odanacatib at most only modestly (15.9%) reduces bone formation rate with long term therapy.