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

Stefan Zajic1, Julie A. Stone1, David Jaworowicz2, Albert Leung1, Le Thi Duong1, Julie Passarelli2, Jill Fiedler-Kelly2, Dosinda Cohn1, Nadia Verbruggen1, and Aubrey Stoch1
1Merck Research Laboratories, 770 Sunnymount Pk, West Point, PA, USA 19486
2Cognigen Corporation, 395 South Youngs Road, Buffalo, NY 14221-7031

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 amino-terminal 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 over 3-year treatment at higher doses
- Elevated uNTx after cessation of treatment and associated LS-BMD changes
- Non-monomotonic 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 2: Schematic of Odanacatib PK/PD Model

Semi-mechanistic PK/PD Model (cont)

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.

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.

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

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-monomotonic dose-response relationship.

Conclusion
- The model supports that a combination of drug effects on bone resorption (E_{rr} 70.4%, EC_{50} 41.7 nM) and osteoclast cycling (E_{IMAX} 74.3%, EC_{50} 19.3 nM) can generate the range of behaviors observed in the Phase II data, including a non-monomotonic 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.