Multiscale Systems Biology / Pharmacology Models (Figure 1)  
- Multi-scale systems approach to pharmacology  
- Serve as a link between preclinical investigation (e.g., disease, genetic variation)  
- Multi-system physiology model (MSPM) includes pharmacologic effects  

MSPM of Bone Mineral Homeostasis and Remodeling (Remodeling, Figure 2)  
- Calcium homeostasis in bone remodeling  
- Bone turnover marker (BTMs): 
  - Bone-specific alkaline phosphatase (BSAP)  
  - C-terminal telopeptide of type I collagen (CTx)  
  - Total hip bone mineral density (BMD)  
- Osteoclast activity: 
  - RANKL–RANK receptor interaction  
  - Integrins, matrix metalloproteinases (MMPs)  
- Osteoblast activity: 
  - TGF-beta (e.g., TGF-beta-1, TGF-beta-2, TGF-beta-3)  
  - Parathyroid hormone (PTH)  
- Pharmacologic effects: 
  - Calcitriol (active Vitamin D)  
  - Cytokines (e.g. TGF beta)  
  - GnRH receptor modulators  

RESULTS – MSPM QUALIFICATION USING CLINICAL DATA: From Two Randomized, Double-Blind, Placebo-controlled, Multi-dose Studies  
- MSPM predictions were in close agreement with observed data: Mean absolute percentage error=9.1%; Mean percentage error=-7.9%  

METHODS – MSPM DEVELOPMENT: BSAP, CTx, BMD  
- BSAP and CTx were modeled using nonlinear mixed-effects models (NLMEM)  
- The MSPM was extended to include BMD changes and was validated using data from denosumab clinical trials  

DISCUSSION  
- The MSPM was validated using data from two independent clinical trials  

REFERENCES  