Quantification of postmenopausal osteoporosis population: An system pharmacology approach using bisphosphonates.

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Objectives: Costly and lengthy clinical trials hinder the development of safe and effective treatments for postmenopausal osteoporosis (PMO). To streamline the development process, our aim was to establish a mechanism-based drug-disease model (MBDDM) that links changes in biomarkers to drug treatment and disease progression based on the underlying bone (patho)physiology.

Methods: A 2-year phase III clinical trial of zoledronic acid (ZA) dataset of 581 postmenopausal women was used to inform the MBDDM in NONMEM 7.2. The MBDDM was linked to clinical trial biomarker data, i.e. the activity of bone removing cells (osteoclasts) to the formation of serum c-terminal telopeptide (sCTX) and the activity of bone forming cells (osteoblasts) to the formation of bone specific alkaline phosphatase (BSAP). The combined activity of osteoclasts and osteoblasts is reflected by changes in bone mineral density (BMD). An exploratory analysis was conducted to identify if a correlation between biomarkers either alone or in combination and fractures exists in a phase III ibandronate efficacy and safety trial in PMO women.

Results: The model was able to simultaneously characterize all biomarker data reasonably well (Figure 1). Exploratory analysis results indicated that in isolation, none of the evaluated biomarkers (BMD, BSAP, sCTX) correlated well with observed fracture events. However, in combination (BSAP-NTX) treatment, suggests that excessive and prolonged suppression of the natural bone turnover may be related to increased fracture risk.

Conclusions: We developed a MBDDM that linked changes in BSAP and sCTX to changes in BMD from baseline as a function of disease progression and response to bisphosphonate treatment. Based on the exploratory results, the model can be further expanded to fracture risk in order to be able to predict changes in the pivotal study endpoint based on short-term clinical biomarker data.
Figure 1: Change from baseline plots for 4 different clinical biomarkers obtained from a phase III pivotal zoledronic acid: BSAP (panel A), CTX (panel B), BMD in lumbar spine (panel C), and BMD in total hip (panel D). The dynamics of the various biomarkers, i.e. CTX is the fastest, BSAP second, and BMD being the slowest are captured respectively. Symbols represent the observed clinical data as well as associated variability; whereas the solid line represents the mean of the model-based predictions and the dashed lines the associated variability with the model based predictions.