Development of a mechanism-based drug-disease model to quantify postmenopausal osteoporosis

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Disclaimer

- We have no conflicts of interest.

- The opinions expressed in this presentation are ours and do not necessarily reflect the official views of the USFDA.

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Introduction

Osteoporosis is a chronic disorder with bones weakening over time. It is more prominent in women due to steep declines in estrogen after menopause.

Current problems in drug development in osteoporosis:
Osteoporosis drug development trials are long and large sample size is needed to evaluate current endpoints such as fracture risk or bone mineral density (BMD) change.

- Phase 3 trials with fracture risk as efficacy endpoint take 2-3 years.
- Phase 2 dose-finding trials with BMD as endpoint take 1-2 years.

Study Objective:
Using bone resorption marker (e.g. CTX) and bone formation marker (e.g. BSAP) data for long term predictions to shorten the trials.
Pharmacokinetics

Drug disease model using bone physiology as link between PK & PD

Pharmacodynamics

Slow biomarker(s)

Outcome

Fast biomarker(s)

Hours
Months
Years
Adapted from: Lemaire V. et al. 2004; Schmidt et al. (2011); Post et al. (2013)
Mechanism-based drug-disease model development workflow

**Disease model**
- Data from postmenopausal osteopenic patients (n=202).
- Saline infusions with calcium (500 mg) and vitamin D (400 IU).

**Drug disease model for bisphosphonates**
- Data from postmenopausal osteopenic patients (n=379).
- Zoledronic acid (5 mg) given either at start of 1st year or at start of 1st and 2nd year with calcium and vitamin D.

**Model Evaluation**
- Data from postmenopausal osteoporotic patients (n=7736).
- Saline infusions with calcium and vitamin D.
- Zoledronic acid (5 mg) given at start of 1st year and start of 2nd year with calcium and Vitamin D.

Software: Nonmem 7.2
Model Equations

**Model Core**

\[
\begin{align*}
\frac{dB}{dt} &= k_B(\sigma(C) - B) \\
dC &= D_A \pi_C (1) \left( \frac{1 + \beta R_0}{1 + \beta R_0 E^\theta \sigma^2(C)} E_C B - (C)(1 + E_{Bis})C \right)
\end{align*}
\]

**Estrogen Decline**

\[
\frac{dE}{dt} = k_{in,E} - k_{out,E} \times E
\]

**BTM & BMD**

\[
\begin{align*}
\frac{dBSAP}{dt} &= k_{in,BSAP} \times B - k_{out,BSAP} \times BSAP \\
\frac{dCTX}{dt} &= k_{in,CTX} \times C - k_{out,CTX} \times CTX \\
\frac{dBMD}{dt} &= k_{in,BMD} \times B - k_{out,BMD} \times C \times BMD
\end{align*}
\]

Model core describes interplay between bone forming (B) and bone resorbing (C) cells under healthy, diseased and therapeutic intervention.

Describes disease trajectory based on decline of endogenous estrogen levels.

Links mechanism based model core to clinically relevant biomarkers.
Performance of Drug-Disease Model for Zoledronic Acid

Model showed reasonably accurate prediction on clinically relevant biomarkers.
Future work

Bone Formation marker (BSAP)

Bone Resorption marker (CTX)

Glucocorticoids
Vitamin D
Calcium
Bisphosphonates
Estrogen, SERMs
RANKL Antibodies

Bisphosphonates

Bone Mineral Density

Fracture risk

Summary

• The drug disease model previously developed based on SERM data could be used to model bisphosphonate data.

• The model quantitatively linked BTM (BSAP, CTX) to BMD via underlying cellular dynamics and can potentially be used to predict BMD changes for longer periods of time.

• Our model could characterize disease progression and disease intervention through therapy.

• This model will be developed further to predict fracture risk and expanded to a bisphosphonate specific model or a generic disease model.
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Backup Slides
Legend for model schematic

- RANK: Receptor Activator for Nuclear Factor Kappa-β
- RANKL: Receptor Activator for Nuclear Factor Kappa-β ligand
- OPG: Osteoprotegerin
- TGF-β: Transforming Growth Factor - β
- EST: Estrogen
- PTH: Parathyroid hormone
- R_u: Uncommitted osteoblast progenitors
- R: Responding osteoblasts
- B: Osteoblasts
- Cp: Osteoclast precursors
- C: Osteoclasts
- BSAP: Bone specific alkaline phosphatase
- CTX: C-telopeptide.
Legend for differential equations

\[
\begin{align*}
\frac{dB}{dt} &= k_B (\sigma(C) - B) \\
\frac{dC}{dt} &= D_A \pi_C (1) \left( \frac{1 + \beta R_0}{1 + \beta R_0 \sigma^2(C)} y - \sigma(C) C \right) \\
\beta &= \frac{RANKL_{\text{unbound}} \times OPG}{RANKL_{\text{Total}} \pi_p}
\end{align*}
\]

where \( \pi_p \) is PTH receptor occupancy. OPG \( \propto \) Estrogen.

**Estrogen**

\[
\begin{align*}
\frac{dE}{dt} &= k_{in,E} - k_{out,E} \times E \\
k_{in,E} &\propto \frac{k_{out,E}}{Age \times YSM}
\end{align*}
\]

**DB**: Differentiation rate of active osteoblasts

**k_B**: Elimination rate of active osteoblasts

**DA**: Osteoclast apoptosis rate due to TGF-β

**πC**: TGF-β receptor occupancy

**σC**: Normalized TGF-β receptor occupancy

**β**: Accounts for unbound RANKL

**k_{in,E}**: Estrogen formation rate

**k_{out,E}**: Estrogen depletion rate

**AGE**: Age of individual

**YSM**: Years since menopause
Legend for differential equations

\[
\begin{align*}
\text{BSAP} & : \text{Baseline BSAP} \\
\text{CTX} & : \text{Baseline CTX} \\
\text{LSBMD} & : \text{Baseline lumbar spine BMD}
\end{align*}
\]

BTM & BMD

\[
\begin{align*}
\frac{dBSAP}{dt} &= k_{in,BSAP} \times B - k_{out,BSAP} \times BSAP \\
\frac{dCTX}{dt} &= k_{in,CTX} \times C - k_{out,CTX} \times CTX \\
\frac{dLSBMD}{dt} &= k_{in,LSBMD} \times B - k_{out,LSBMD} \times C \times LSBMD
\end{align*}
\]

\[
\begin{align*}
k_{in,BSAP} &= k_{out,BSAP} \times BSAP_0 \\
k_{in,CTX} &= k_{out,CTX} \times CTX_0 \\
k_{in,LSBMD} &= k_{out,LSBMD} \times LSBMD_0
\end{align*}
\]

\[
\begin{align*}
k_{in,BSAP} & : \text{BSAP formation rate} \\
k_{out,BSAP} & : \text{BSAP depletion rate} \\
k_{in,CTX} & : \text{CTX formation rate} \\
k_{out,CTX} & : \text{CTX depletion rate} \\
k_{in,LSBMD} & : \text{LSBMD increase rate} \\
k_{out,LSBMD} & : \text{LSBMD decrease rate.}
\end{align*}
\]