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.

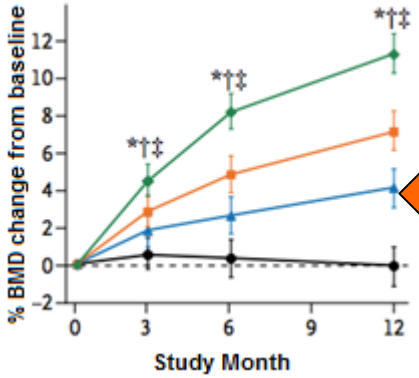
Pharmacokinetics

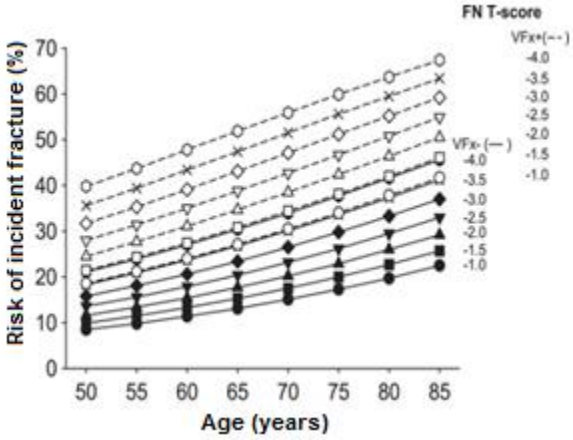
Pharmacodynamics

Slow biomarker(s)

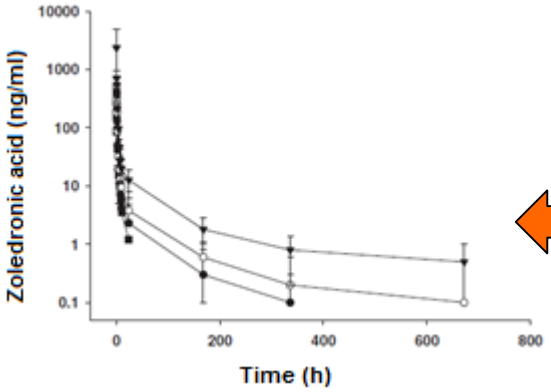
Outcome

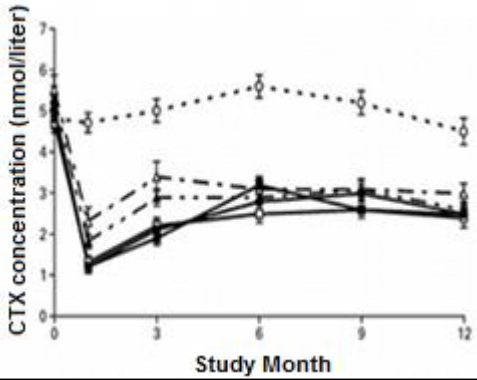
Drug disease model using bone physiology as link between PK & PD





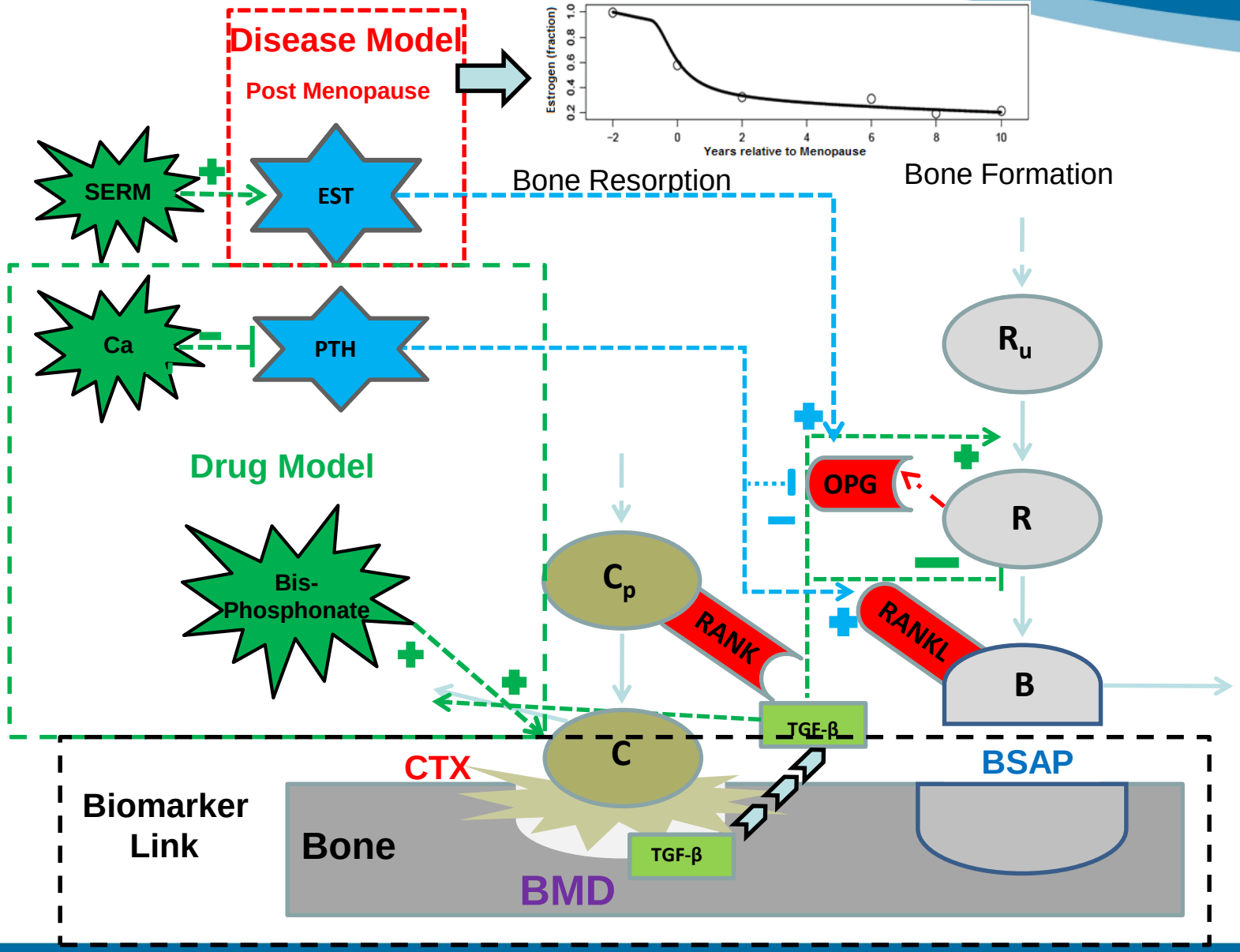
Fast biomarker(s)





Hours | Months | Years

Schematic of model



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

$$\begin{cases} \dfrac{dB}{dt} = k_B(\sigma(C) - B) \\ \dfrac{dC}{dt} = D_A \pi_C(1)\left(\dfrac{1+\beta R_0}{1+\beta R_0 E^{\theta}\sigma^2(C)} E_{Ca} B - \sigma(C)(1+E_{Bis})C \right) \end{cases}$$

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

Estrogen Decline

$$\begin{cases} \dfrac{dE}{dt} = k_{in,E} - k_{out,E} \times E \end{cases}$$

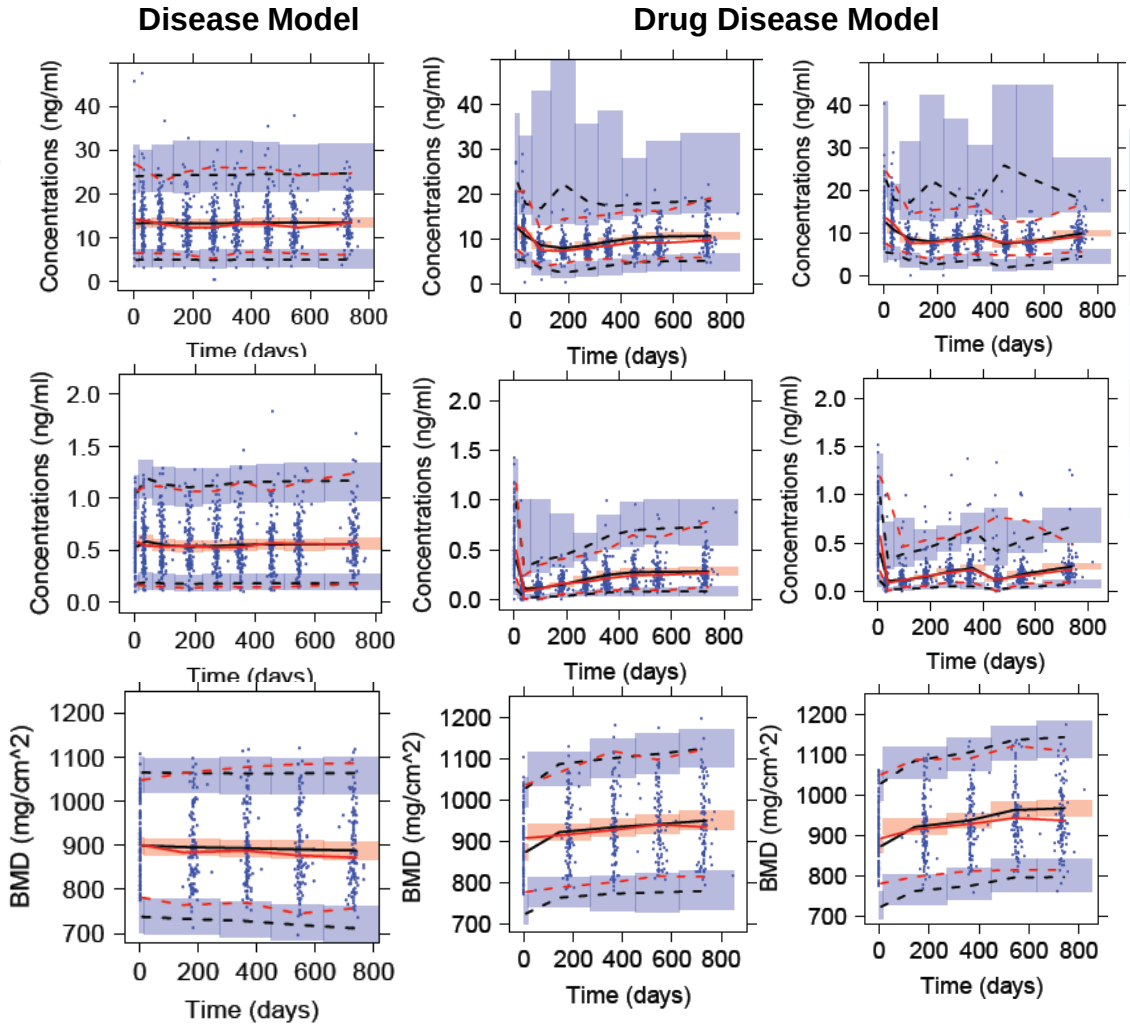
Describes disease trajectory based on decline of endogenous estrogen levels.

BTM & BMD

$$\begin{cases} \dfrac{dBSAP}{dt} = k_{in,BSAP} \times B - k_{out,BSAP} \times BSAP \\ \dfrac{dCTX}{dt} = k_{in,CTX} \times C - k_{out,CTX} \times CTX \\ \dfrac{dBMD}{dt} = k_{in,BMD} \times B - k_{out,BMD} \times C \times BMD \end{cases}$$

Links mechanism based model core to clinically relevant biomarkers.

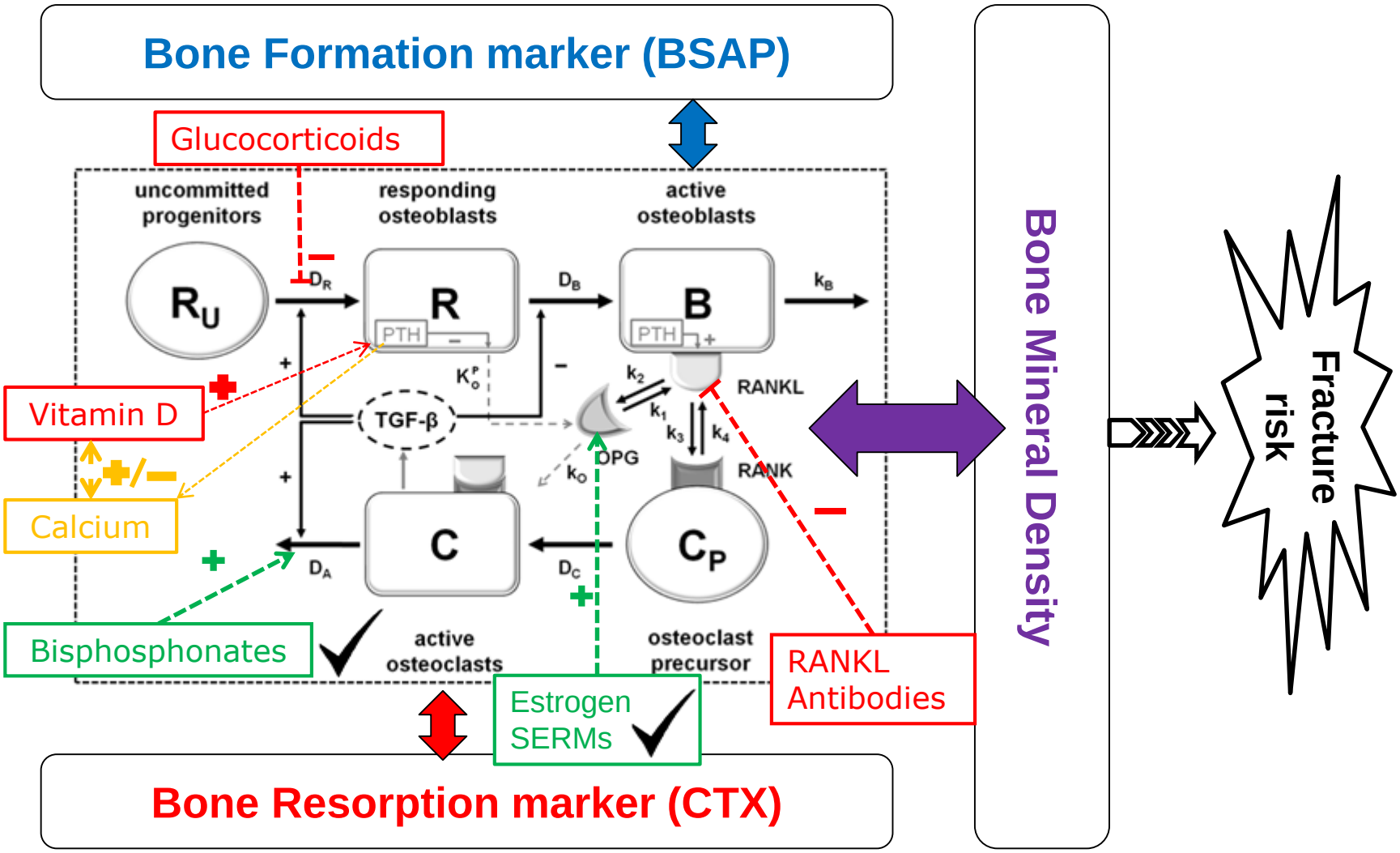
Performance of Drug-Disease Model for Zoledronic Acid



Inter-individual variability	Covariates
Biomarker Baseline	BMI
Drug Clearance	Race
Drug Effects	Age
	YSM

Model showed reasonably accurate prediction on clinically relevant biomarkers.

Future work


Bone Formation marker (BSAP)
Glucocorticoids
uncommitted progenitors
responding osteoblasts
active osteoblasts
R_U
R
B
D_R
D_B
k_B
PTH
K_O^P
TGF-β
Vitamin D
Calcium
Bisphosphonates
C
C_P
D_A
D_C
active osteoclasts
osteoclast precursor
k_2
k_1
k_3
k_4
RANKL
RANK
OPG
k_O
Estrogen SERMs
RANKL Antibodies
Bone Resorption marker (CTX)
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

$$\begin{cases} \frac{dB}{dt} = k_B(\sigma(C) - B) \\ \frac{dC}{dt} = D_A \pi_C(1)\left(\frac{1+\beta R_0}{1+\beta R_0 \sigma^2(C)} y - \sigma(C)C\right) \end{cases}$$

$$\beta = \frac{RANKL_{unbound}}{RANKL_{Total}} \times \frac{OPG}{\pi_P}$$

where π_P is PTH receptor occupancy.
OPG $\propto$ Estrogen.

Estrogen

$$\begin{cases} \frac{dE}{dt} = k_{in,E} - k_{out,E} \times E \\ k_{in,E} \propto \frac{k_{out,E}}{Age \times YSM} \end{cases}$$

D_B: Differentiation rate of active osteoblasts

k_B: Elimination rate of active osteoblasts

D_A: Osteoclast apoptosis rate due to TGF-β

π_C: TGF-β receptor occupancy

σ_C: 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

$BTM \ \ \& \ \ BMD$

$$\begin{cases} \dfrac{dBSAP}{dt} = k_{in,BSAP} \times B - k_{out,BSAP} \times BSAP \\ \dfrac{dCTX}{dt} = k_{in,CTX} \times C - k_{out,CTX} \times CTX \\ \dfrac{dLSBMD}{dt} = k_{in,LSBMD} \times B - k_{out,LSBMD} \times C \times LSBMD \end{cases}$$

$$k_{in,BSAP} = k_{out,BSAP} \times BSAP_0$$

$$k_{in,CTX} = k_{out,CTX} \times CTX_0$$

$$k_{in,LSBMD} = k_{out,LSBMD} \times LSBMD_0$$

$k_{in,BSAP}$: BSAP formation rate

$k_{out,BSAP}$: BSAP depletion rate

$k_{in,CTX}$: CTX formation rate

$k_{out,CTX}$: CTX depletion rate

$k_{in,LSBMD}$: LSBMD increase rate

$k_{out,LSBMD}$: LSBMD decrease rate.

$BSAP_0$: Baseline BSAP

CTX_0 : Baseline CTX

$LSBMD_0$: Baseline lumbar spine BMD