# Application of a Multiscale Physiologically-Based Bone and Calcium Systems Model to Guide the Development of GnRH receptor modulators for the Management of Endometriosis

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## Abstract

**Objectives:** *To provide model-based decision support toward the selection of doses, endpoints and study durations for gonadotropin releasing hormone (GnRH) antagonist clinical programs intended for the management of endometriosis (EM).*

**Methods:** *A previously reported, multiscale physiologically-based calcium homeostasis and bone remodeling model [1] that had been adopted to describe the effects of estrogen loss during menopause transition.[2] Longitudinal effects of varying estradiol (E2) reductions caused by GnRH suppression on biomarkers of bone turnover (BM) and bone mineral density (BMD) changes were simulated from the bone model.[1] The relative percent decreases in E2, assuming a baseline concentration of 100 pg/mL, affected by varying degrees of GnRH inhibition were used to fit a differential equation linking bone marker changes with BMD effects to publicly available elagolix,[3, 4] leuprolide [5, 6, 7] and triptorelin [8] data using Berkeley Madonna (version 8.0.1, University of California at Berkeley). These results were used to determine if early (1–3 months) E2 and/or specific BM changes were predictive of 6-month BMD changes, thereby guiding which endpoints to consider and the treatment duration that would provide informative changes in the endpoint(s). A larger literature-based database (publication years 1988–2006) that included clinical study-level summary data from GnRH agonist treatments (leuprolide, nafarelin, triptorelin, and goserelin) was used to provide an external evaluation of the 6-month BMD predictions from the multiscale model. Additionally, a logistic regression model describing the relationship of estrogen and EM-related pain (total endometrial symptom severity score, ESSS) was fit to patient-level data from three clinical studies using WinBUGS 1.4.[9] Each of the three studies investigated nafarelin (200 mcg bid) administered for 3 or 6 months to EM patients (n=499). ESSS total score was categorized with increasing pain as (0, 1, 2, 3, 4, and $>$ 4). The resulting beneficial effect of GnRH inhibition on reduced EM pain was used in conjunction with the potential detrimental effect of BMD loss to characterize a therapeutic index to guide dose selection for clinical studies. Ideally, a target E2 level would be determined to result in decreased endometrial pain severity while minimizing effects on BMD. For reference, the elagolix primary endpoint for 6-month BMD, pursuant to discussion with FDA, was prespecified as the lower bound of 95% CI to show no greater loss than $-2.2\%$ [4], presumably to conclude a no effect boundary.*

**Results:** *Clinical data indicated that suppression of E2 through GnRH-mediated effects (either agonism or antagonism) occurs within the first month of treatment. Observed median E2 decreased to approximately 41 pg/mL and 21 pg/mL following 6 months of treatment with elagolix 150 mg and 250 mg QD, respectively [3,4], with corresponding BMD changes from baseline at 6 months of 0.8% and 1.6%, respectively. From the literature database, median E2 following full suppression with GnRH agonists was typically near or below 10 pg/mL with corresponding 6-month BMD decreases of 3-5%. Bone markers showed an increase at 6 months in bone specific alkaline phosphatase (BSAP) and serum c-telopeptide (CTX) of 39% and 88%, respectively.[8] BM and BMD model predictions (Table 1) were consistent with these observed data. The model results indicated that bone marker changes are delayed compared to the E2 decrease. In addition, within the range of acceptable 6-month BMD changes (e.g., $-0.8\%$ up toward $-1.6\%$), there was minimal early differentiation of BM across doses. An extension of the model prediction across a continuous range of 10–80 pg/mL adequately predicted the broader literature database, indicating that E2 was a reliable predictor of 6-month BMD. The logistic regression indicated that approximately 15% of patients with E2 $>$ 80 pg/mL were expected to have an ESSS=0, whereas P(ESSS=0) increased to 26% and 29% at E2 values of 40 and 20 pg/mL, respectively.*

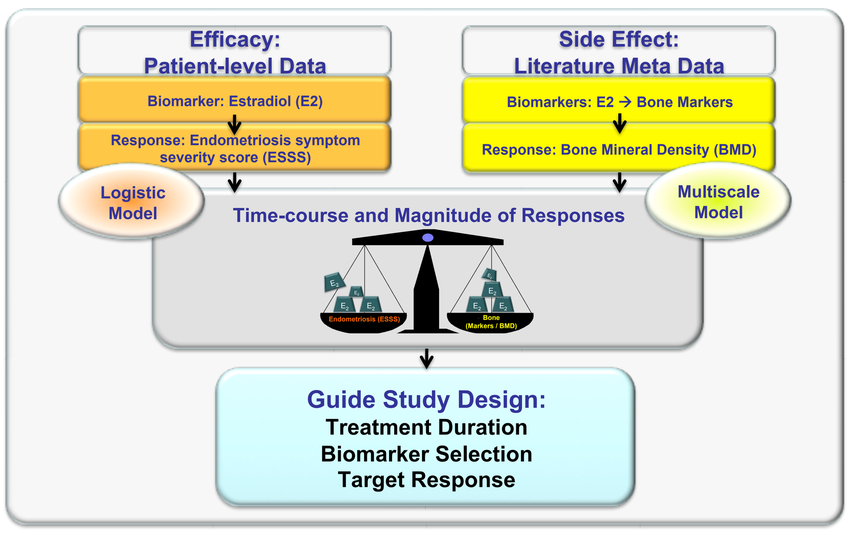
**Conclusions:** *E2, measured as early as 1–2 months after treatment initiation, was shown to be a reliable predictor of 6-month BMD change, whereas bone markers, as affected through GnRH inhibition, were projected to change too slowly to provide reliable dose differentiation earlier than at least 3-month study duration. Doses within a GnRH antagonist development program that target E2 in the range of $>$ 20= to 40 pg/mL are expected to provide efficacious EM pain response while minimizing BMD effects. Overall, our model-based approach provides a quantitative framework for preclinical and clinical research efforts focused on mechanisms that modulate E2 levels.*

## Objective

Provide model-based decision support for gonadotropin releasing hormone (GnRH) modulator programs intended for the management of EM:

1. Establish quantitative relationship between estradiol (E2) and endometriosis efficacy endpoints
2. Predict the consequences of these E2 levels required for efficacy on Bone Mineral Density (BMD)
3. Explore alternative (shorter) study designs using Bone Markers (BM) to predict for long-term BMD effects

## Methods



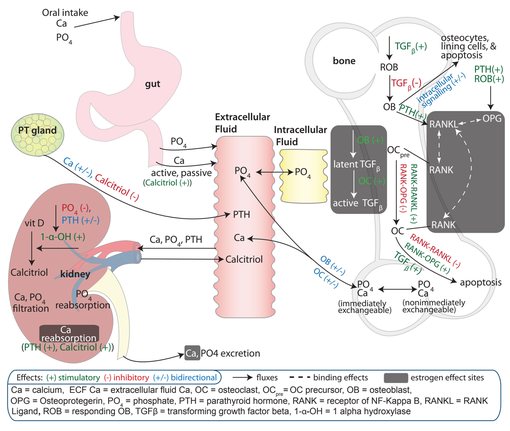

### Data

- **Bone Markers and Bone Mineral Density (summary level literature data)**
  - Estimation Dataset
    - Full GnRH suppression: leuprolide [5, 6, 7] and triptorelin [8]
    - Partial GnRH suppression: elagolix [3, 4]
    - Assumed E2 baseline concentration of 100 pg/mL
      - E2 $\rightarrow$ 10 pg/mL (90% depletion) $\sim$ full GnRH suppression
      - E2 $\rightarrow$ 20 pg/mL (80% depletion) $\sim$ elagolix 250 mg QD
      - E2 $\rightarrow$ 40 pg/mL (60% depletion) $\sim$ elagolix 150 mg QD
  - Evaluation Dataset (13 studies, publication years 1990–2006)
    - GnRH agonist treatments (leuprolide, nafarelin, triptorelin, and goserelin)
    - Provided external evaluation of the 6-month BMD predictions
- **ESSS Efficacy Data (patient level, Pfizer data)**
  - Three clinical studies
  - Nafarelin (200 mcg bid) administered for 3 or 6 months to EM patients (n=499)

### Models

- **Bone Markers and Bone Mineral Density**
  - Existing Multiscale Physiologically-Based Model Describes E2 and BM Relationship[1, 2] (*Figure 1*)
    - Osteoclast function (resorption) marker: serum cross-linked C-telopeptide of type I bone collagen (CTx).
    - Osteoblast function (formation) marker: bone specific alkaline phosphatase (BSAP)
  - Estimate BM Effect on Lumbar Spine BMD (*Equation 1*)
  - Determine if Early (1–3 months) E2 and/or BM Changes Predicted 6-month BMD

*Figure 1: Calcium and Bone Multiscale Model*




Modified from Figure 1 of Peterson and Riggs, 2010 [1]

- **Efficacy: ESSS**
  - Ordered Categorical Logistic Regression Model
  - Estimate E2 and ESSS Relationship
  - ESSS Increased with Pain as (0, 1, 2, 3, 4, and $>$ 4)
  - Determine Target E2 Levels with Satisfactory Efficacy

### Software

- Literature data digitized: Plot Digitizer 2.4.1 (http://plotdigitizer.sourceforge.net/)
- Graphics and data management: R version 2.10.1 (http://r-project.org)
- Multiscale model fitting and simulation: Berkeley Madonna 8.0 (http://berkeleymadonna.com)
- Logistic regression: WinBUGS 1.4 [9]

## Results

- **Bone Markers and Bone Mineral Density**
  - Equation (1): Link bone markers with BMD

$$\frac{d(BMD)_{LS}}{dt} = k_{in,BMD} \cdot \left(\frac{\text{BSAP}}{\text{BSAP}_{\text{baseline}}}\right)^{\gamma_{OB}} - k_{out,BMD} \cdot \left(\frac{CT_x}{CT_{x_{baseline}}}\right)^{\gamma_{OC}} \cdot BMD_{LS} \quad (1)$$

$$\gamma_{OB} = 0.0739; \quad \gamma_{OC} = 0.14; \quad k_{\text{out,BMD}} = 0.000397 \text{ h}^{-1}$$

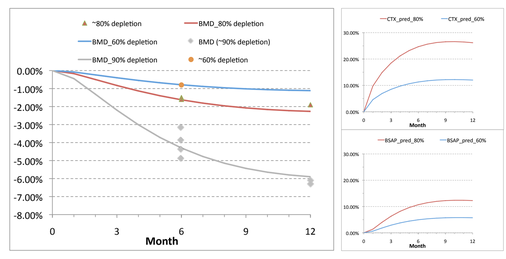
  - BM and BMD model predictions (*Table 1, Figure 2*)

*Table 1: Model Predicted BM and BMD Changes from Baseline*

| E2 (pg/mL) | Month | BSAP | CTX | BMD |
|---|---|---|---|---|
| 10 | 1 | 5.1% | 28.4% | −0.5% |
| | 3 | 22.7% | 60.3% | −2.2% |
| | 6 | 38.0% | 84.0% | −4.3% |
| 20 | 1 | 1.4% | 9.8% | −0.2% |
| | 3 | 6.3% | 18.5% | −0.8% |
| | 6 | 10.7% | 24.7% | −1.6% |
| 40 | 1 | 0.63% | 4.6% | −0.1% |
| | 3 | 2.9% | 8.5% | −0.4% |
| | 6 | 5.9% | 11.3% | −0.8% |

Complete (10 pg/mL); partial (20, 40 pg/mL) E2 suppression; baseline E2: 100 pg/mL

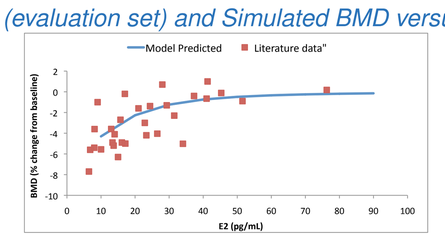
*Figure 2: Observed and Predicted BMD and Bone Markers versus Time*




Multiscale model predictions (lines) and observed literature data (symbols).

- Range of acceptable 6-month BMD changes (e.g., $-0.8\%$ up toward $-1.6\%$)
  - Minimal early differentiation of BM and BMD across doses
  - BM changes are delayed compared to the E2 decrease
- Literature evaluation dataset for E2 and BMD (*Figure 3*)
  - Model prediction across a continuous range of 10–80 pg/mL
  - Predicted the broader literature database
  - Supported E2 as reliable predictor of 6-month BMD.

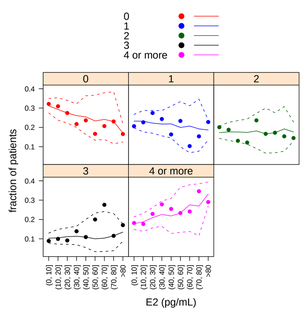
*Figure 3: Observed (evaluation set) and Simulated BMD versus E2*




Multiscale model simulations (lines) and observed literature meta data (symbols).

- **Efficacy: ESSS**

*Figure 4: Predicted ESSS versus E2*




  - P(ESSS=0 | E2 $>$ 80 pg/mL) $\sim$ 15%
  - P(ESSS=0) increased to 26% and 29% at E2 = 40 and 20 pg/mL, respectively
  - P(ESSS$\geq$4) decreased from 27% $\rightarrow$ 19% as E2 decreased (80 $\rightarrow$ 20 pg/mL)

Predictions from ordered categorical logistic regression model

- **Efficacy versus Side Effect**

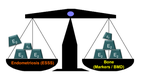
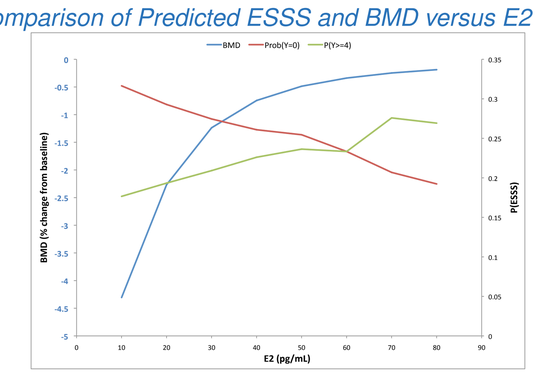


*Figure 5: Comparison of Predicted ESSS and BMD versus E2*




ESSS model predictions from ordered categorical logistic regression model; BMD prediction from multiscale model.

## Conclusion

- E2, measured as early as 1–2 months after treatment initiation, was shown to be a reliable predictor of 6-month BMD change.
- Bone markers, as affected through GnRH inhibition, were projected to change too slowly to provide reliable dose differentiation earlier than at least 3-month study duration.
- GnRH receptor modulation targeting E2 in the range of $>$ 20 to 40 pg/mL are expected to provide efficacious EM pain response while minimizing BMD effects (*Figure 5*).
- Model-based approach has provided a quantitative framework for preclinical and clinical research efforts focused on mechanisms that modulate E2 levels.

## References

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