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ARTICLE

Validation of a quantitative systems pharmacology model of calcium homeostasis using elagolix Phase 3 clinical trial data in women with endometriosis

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Abstract

Elagolix is a novel, oral gonadotropin-releasing hormone receptor antagonist indicated for the management of moderate to severe pain associated with endometriosis and heavy menstrual bleeding associated with uterine fibroids. Consistent with its mechanism of action, elagolix exhibited dose-dependent suppression of estradiol (E2) in clinical studies. A dose-response model that describes the relationship between elagolix dosages and average E2 levels was combined with a previously published quantitative systems pharmacology (QSP) model of calcium homeostasis to predict bone mineral density (BMD) changes during and following elagolix treatment. In the QSP model, changes in E2 levels were linked to downstream changes in markers of bone resorption (carboxyterminal cross-linked telopeptide of type 1 collagen [CTX]), formation (N-terminal propeptide of type 1 procollagen [P1NP]) and BMD. The BMD, CTX, and P1NP predictions by the QSP model were validated against observed data from four phase III clinical trials of elagolix in premenopausal women with endometriosis. BMD, CTX, and P1NP were successfully described by the QSP model, without any model fitting, suggesting that the model was validated for further predictions of elagolix effects on BMD. Simulations using the validated QSP model demonstrated that elagolix 150 mg once daily dosing for 24 months is predicted to result in −0.91% change from baseline in lumbar spine BMD. The QSP model simulation results were part of the totality of evidence to support the approved duration of therapy for elagolix 150 mg once daily in patients with endometriosis.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Medical therapies that suppress estrogen, such as gonadotropin-releasing hormone (GnRH) receptor agonists/antagonists, result in hypoestrogenic effects, such as loss of lumbar spine bone mineral density (BMD), which restricts the duration of use, leading to potential loss of therapeutic benefits to the patient over time.

Trial registration: ClinicalTrials.gov identifiers: NCT01620528 (EM-1), NCT01760954 (EM-III), NCT01931670 (EM-II), NCT02143713 (EM-IV).

WHAT QUESTION DID THIS STUDY ADDRESS?

Can a quantitative systems pharmacology model of calcium homeostasis predict BMD and bone biomarker changes during and post GnRH therapy (e.g., with elagolix)?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This study provided independent, external validation on BMD changes and mechanistic foundation of a previously published model using observed clinical data.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

This study provides further evidence of the value of model-informed drug development through modeling of estrogen levels during elagolix treatment, and simulations of BMD and bone biomarker changes according to elagolix dose. Benefit/safety assessments for patients seeking estrogen suppressing therapies can be predicted for the duration of treatment and beyond clinical study durations (>12 months).

INTRODUCTION

Endometriosis is a chronic, estrogen-dependent inflammatory disease that results from implantation of endometrial-like tissue outside the uterus and affects ~ 6–10% of women of reproductive age.[1] Gonadotropin-releasing hormone (GnRH) receptor agonists are being used as a medical treatment option to avoid surgery; however, these agents can cause an initial flare of symptoms followed by significant hypoestrogenic effects, such as hot flush and bone mineral density (BMD) decreases, which led to a restricted duration of use.[2]

Elagolix, an orally active, nonpeptide GnRH antagonist, has recently been approved for the management of moderate to severe pain associated with endometriosis[3–5] and heavy menstrual bleeding associated with uterine fibroids.[6–8] Elagolix mechanism of action via inhibition of GnRH receptors at the posterior pituitary leads to dose-dependent suppression of sex hormones, such as estradiol (E2).[9,10] In two 6-month, phase III clinical trials (Elaris Endometriosis [EM]-I[11] and EM-II[12]) with 6-month extension studies (Elaris EM-III and EM-IV),[13] elagolix doses of 150 mg once-daily (q.d.) and 200 mg twice-daily (b.i.d.) reduced dysmenorrhea and nonmenstrual pelvic pain in premenopausal women with moderate to severe pain associated with endometriosis, and dose-dependent changes in BMD were observed with both the elagolix dosages.[3,13] During the Elaris clinical studies, the lumbar spine, total hip, and the femoral neck were monitored for BMD changes associated with elagolix treatment. It was observed that all three regions correlated well, with the lumbar spine being the most sensitive of the three regions to BMD changes (largest change from baseline).[14] In the Elaris EM-I and EM-II studies, elagolix 150 mg q.d. treatment groups showed mean changes from baseline in lumbar spine BMD at month 6 of −0.32% and −0.72%, respectively.[3] The elagolix 200 mg b.i.d. treatment groups showed mean changes from baseline in lumbar spine BMD at month 6 of −2.61% and −2.49% in the Elaris EM-1 and EM-II studies, respectively.[3]

A previously published physiologically based mathematical model of integrated calcium homeostasis and bone biology by Peterson and Riggs[15] and the subsequent extension by Riggs et al.[16] included several physiologic compartments such as the gut, vasculature, kidneys, parathyroid gland, bones, and osteoblasts/osteoclasts to describe bone remodeling processes with BMD as the clinical end point. This quantitative systems pharmacology (QSP) model has been utilized to identify optimal dosing regimens to maximize and maintain BMD following treatment with the osteoporosis therapy, romosozumab,[17] and by the US Food and Drug Administration (FDA) to evaluate alternative dosing regimens for parathyroid hormone (NATPARA).[18] To evaluate the utility of the QSP model in predicting the observed changes in BMD with elagolix treatment in patients with endometriosis and to conduct simulations beyond the duration of the phase III clinical trials (>12 months), the existing QSP model structure and components were directly applied, as published by Riggs et al.[16] We report here the implementation, validation, and application of the QSP bone model to the lumbar spine region as an example of model-informed drug development (MIDD). The results herein assisted in supporting the duration of therapy of elagolix for the management of moderate to severe pain associated with endometriosis.[3]

METHODS

Overview

To validate and apply the QSP model to obtain and predict BMD changes throughout and following elagolix treatment, a dose-response model (dose-E2) for elagolix was developed utilizing clinical study data to characterize the dose and E2 relationship. Due to the natural oscillatory dynamics of E2 levels in women[19] (e.g., high diurnal variation compounded

by monthly menstrual cycle fluctuations) and the practicality of making such measurements in the context of phase II and III clinical studies, the variability in observed E2 levels necessitated the use of predicted E2 values from the dose-E2 model for the QSP model input. Working with predicted instead of directly with the observed data also avoided systematic bias that may be introduced when all women were sampled at the beginning of their menstrual cycle in the first months of some but not all studies. Following validation of the QSP model against clinically observed BMD and bone biomarker (carboxyterminal cross-linked telopeptide of type 1 collagen [CTX] and procollagen type 1 N-terminal propeptide [P1NP]) data using predicted E2 values, QSP model simulations were performed to predict BMD changes beyond the clinical study duration (>12 months of continuous dosing).

Data sources

Data from six phase I, II, and III studies were used to develop the exposure-response (dose-E2) model and validate the QSP model predictions for lumbar spine BMD and bone biomarker changes over time. Lumbar spine BMD measurements, E2 levels, and bone biomarker levels were compiled, as available, from a phase I study conducted in healthy premenopausal women,[10] a phase II study conducted in premenopausal women experiencing heavy menstrual bleeding from uterine fibroids,[20] and four phase III studies in premenopausal women experiencing moderate to severe pain associated with endometriosis.[11–13] Details regarding clinical study designs and participant demographics have been published previously for each study.[10–13,20] A summary of these studies is provided in Table 1. The dose-E2 model utilized all study data listed in Table 1. Validation of the QSP model utilized the phase III study data. All studies were conducted in accordance with Good Clinical Practice guidelines and ethical principles that have their origin in the Declaration of Helsinki. Each study protocol was approved by their respective institutional review boards, and written informed consent was obtained from each participant before study-related procedures were performed.

Dose-E2 model

The dose-response model was developed to characterize the relationship between elagolix dosing regimens and E2 levels using (nonlinear) regression. In order to account for different population sizes and sampling frequencies across the different studies, a weighted least-squares approach for the nonlinear regression was used, where each dosing regimen was weighted with the number of patients in each cohort.

TABLE 1 Elagolix clinical studies and data included in the QSP validation

Study description	Study design, duration, elagolix dosing regimens	Lumbar spine BMD measurements	Estradiol sampling	Bone biomarker sampling
Phase I				
PK/PD study in healthy premenopausal women[9]	Multiple-dose study for 3 menstrual cycles (84 days); 100/150/200 mg q.d. and 100/200/300 mg b.i.d.	NA	3×/week from screening through cycle 3	Screening, cycle 1 week 1, cycle 3 final visit
Phase IIb				
Uterine fibroids study in premenopausal women[14]	Multiple-dose study for 6 months; 300 mg b.i.d., and 600 mg q.d.	Screening and month 6	Monthly from months 1 to 6	Baseline, months 3 and 6
Phase III				
Endometriosis studies in premenopausal women (EM-I, EM-II, EM-III, and EM-IV)[11–13]	Multiple-dose studies for 6 months; 150 mg q.d. and 200 mg b.i.d.	Baseline and month 6	Monthly from months 1 to 6	Baseline, months 3 and 6

Abbreviations: BMD, bone mineral density; EM, endometriosis studies; ext, extension; NA, not applicable; PK/PD, pharmacokinetic/pharmacodynamic; QSP, quantitative systems pharmacology.

Additionally, a higher weight was given to data from the elagolix phase I study proportional to the more intensive and tightly controlled E2 sampling scheme (12 samples per month compared with 1 sample per month in other studies). Generally, observations were at different times with respect to dosing, but mostly, the concentrations were expected to be at steady-state. After the onset of the initial suppression, daily and monthly variations are expected to have a larger magnitude than variations due to changing the drug concentration over the day.[21]

Multiple nonlinear functions were evaluated to describe the relationship between daily elagolix dose and E2 level. The following relationships were tested:

Linear:

$$\mathrm{E2} = \mathrm{intercept} - \mathrm{slope} * \mathrm{DailyDose} \quad (1)$$

Exponential:

$$\mathrm{E2} = e^{-(\log(\mathrm{intercept}) - \mathrm{slope} * \mathrm{DailyDose})} \quad (2)$$

And shifted/scaled logit:

$$\mathrm{E2} = e^{\mathrm{logE2}_{min}} + \frac{(e^{\mathrm{logE2}_{\max}} - e^{\mathrm{logE2}_{\min}})}{1 + e^{(\mathrm{slope} * \mathrm{DailyDose})}} \quad (3)$$

where $E2_{max}$ and $E2_{min}$ are the upper and lower bounds, respectively, for the model predictions. DailyDose is the total daily dose for elagolix. The final model was selected based on the Bayesian information criterion (BIC), where the model with the lowest BIC was taken forward.

QSP model validation

The QSP model was implemented in R (version 3.6.3) without any modification from the original publication by Riggs et al.[16] The final elagolix dose-E2 model was used to compute the expected E2 suppression with each regimen. The predicted E2 levels were subsequently used as input for the QSP model to predict lumbar spine BMD and bone biomarker (CTX and P1NP) changes following treatment with various elagolix dosing regimens for up to 12 months. In phase III studies, only CTX and P1NP were measured, thus, these analyses were limited to inclusion of only these two bone biomarkers. In the model by Riggs et al.,[16] bone-specific alkaline phosphatase (BSAP) was considered as a measure of osteoblast function/bone formation; however, in our studies, clinical data were not obtained for BSAP while P1NP was collected, which is a recommended biomarker for bone formation.[22,23] The predicted lumbar spine BMD and bone biomarker changes were compared with those observed in the phase II and III studies by overlaying the model predictions with the observed data. In addition, lumbar spine BMD and bone biomarker changes 6 months after stopping 12 months of elagolix treatment were predicted and compared with observed data obtained at the 6-month post-treatment follow-up (PTFU) visits for the Elaris phase III extension study (EM-IV). It should be noted that EM-III was not designed to collect and evaluate post-treatment BMD recovery for all patients, and is therefore not a comprehensive dataset for this application.[14] These comparisons represented external validation of the QSP model and enabled the high-level validation of the lumbar spine BMD predictions, as well as mechanistic validation of the biomarkers.

Simulations

The elagolix dose-E2 model and the QSP model were used to predict scenarios of elagolix treatment in premenopausal women with endometriosis beyond the duration of the phase III clinical trials and included:

1. Continuous treatment with elagolix 150 mg q.d. or 200 mg b.i.d. for 24 months, and
2. Continuous treatment with elagolix 150 mg q.d. or 200 mg b.i.d. for 12 months followed by post-treatment follow-up for 12 months.

RESULTS

Elagolix dose-E2 model

Average E2 levels in premenopausal women at baseline ranged between 80 and 100 pg/ml and decreased nonlinearly down to ~ 10 pg/ml at the highest elagolix doses of 600 mg per day. The observed E2 levels showed increased degrees of variability for lower to medium elagolix doses (100–200 mg total daily dose), consistent with partial suppression of E2 at these doses.[9] The relationship between elagolix dose and E2 levels was best described by a scaled logistic function (Equation 3). The model fit across various elagolix total daily dose is shown in Figure 1. In comparison with linear and exponential (Equations 1 and 2) models, using the inverse logit improved the visual fit as well as the BIC (Table S1). Overall, the nonlinear regression dose-response model for E2 accurately predicted the central trend in median E2 levels following different elagolix dosing regimens (Figure 1). The final model parameter estimates are presented in Table 2. The model parameters were estimated with reasonable precision, as indicated by the low standard errors.

External validation of the QSP model

Figure 2 shows the observed values and model prediction for lumbar spine BMD, CTX, and P1NP at months 6 and

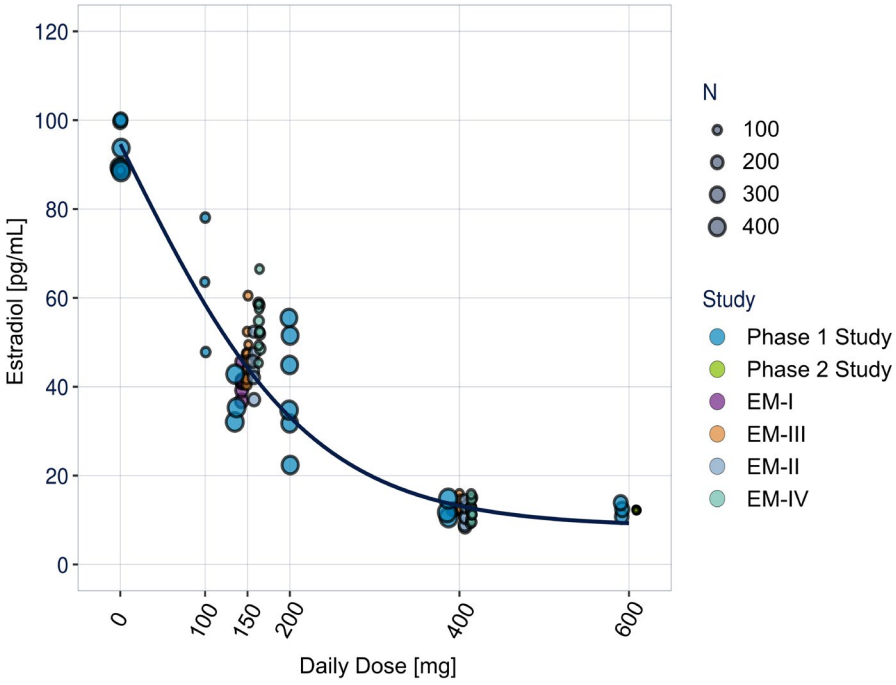

FIGURE 1 Observed and model-predicted estradiol levels in premenopausal women undergoing elagolix treatment. Observed (circles) and fitted (line) estradiol levels are shown. Daily dose is the total daily dose administered. The number of measurements (*N*) is represented by the size of the circle as noted in the legend. See Table 1 for study details. EM, endometriosis studies

TABLE 2 Final parameter estimates for the dose-response nonlinear regression model for estradiol levels

Model parameter	Estimate	Standard error
Slope	0.00894	0.000427
$Log(E2_{max})$	5.20	0.0314
$Log(E2_{min})$	2.14	0.104

Note: The value at zero concentration is $(Exp(log(E2_{max})) + exp(log(E2_{min}))/2$. $E2_{max}$ and $E2_{min}$ are the upper and lower bounds.

12. Across different elagolix doses and resulting levels of E2 suppression, the QSP model predictions adequately captured the trends in the observed data with root-mean-square-errors (RMSE) for lumbar spine BMD at 6 and 12 months of 0.780 and 0.684%, respectively (see Table S2). For CTX, RMSE at 6 and 12 months was 13.1% and 12.3%, respectively; for P1NP, RMSE at 6 and 12 months was 4.39 and 7.09%, respectively. The model slightly overpredicted changes (<1.5% for any single regimen) in lumbar spine BMD at 6 months for high levels of E2 suppression (>85%; Figure 2, left panel). The same behavior was not observed for the 12-month data (Figure 2, right panel).

It was of particular interest to also evaluate the dynamics of the QSP system in cases where elagolix treatment is stopped. In the phase III EM-IV study, data were systematically collected for a 6-month period post-treatment for all patients, making this cohort suitable to validate this aspect of the model. Within the Elaris phase III studies, four treatment sequences occurred for patients participating in the primary trials and extension studies. Women that started on placebo and opted to enroll into the extension study (Elaris EM-III or EM-IV) were randomized to either 150 mg q.d. or 200 mg b.i.d. for the next 6 months and followed up for another 6 months.[13] The resulting longitudinal data are shown in Figure 3 (left panel), together with the respective model predictions for these treatment sequences. The model predictions were in close agreement with the trends of the observed data across lumbar spine BMD, P1NP, and CTX.

The other treatment sequences occurred for women who had received an active treatment regimen and enrolled into the extension study maintaining the same dose (e.g., 150 mg q.d. or 200 mg b.i.d.). The resulting data, covering 12 months of treatment followed by 6 months of PTFU, are also shown in Figure 3 (right panel). For lumbar spine BMD changes, consistent with the overprediction of the change at 6 months and high doses seen in Figure 2 (left panel), we also see faster dynamics from the model initially, which is attenuated at 12 months (Figure 2, right panel). Again, the data after cessation of treatment were adequately described by the model across lumbar spine BMD, CTX, and P1NP datapoints in all treatment sequences. In summary, the QSP model performed well for all on-treatment and post-treatment scenarios, as demonstrated by the visual predictive checks against the observed data, considering that no adjustments to any parameters or model structure components were made.

QSP simulations

Simulations using the QSP model for continuous elagolix dosing for 24 months predicted that lumbar spine BMD changes at 24 months are similar to the lumbar spine BMD change at 12 months of treatment (Figure 4). The

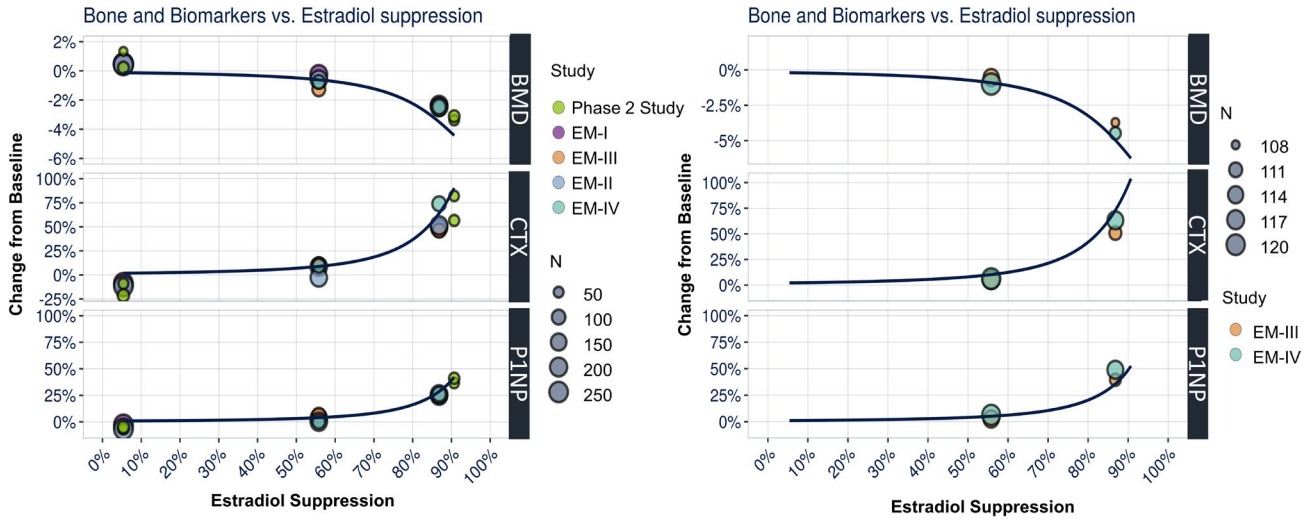

FIGURE 2 Observations and QSP model predictions for changes in BMD and bone turnover biomarkers during treatment with elagolix for 6 and 12 months. Observed values are plotted as circles designated by study in the legend and correspond to month 6 (left panel) and month 12 (right panel). Observed data and study populations are denoted by *N* and are represented by the size of the circle. QSP model predictions are shown as a line. See Table 1 for source data and study information. BMD, bone mineral density; CTX, carboxyterminal cross-linked telopeptide of type 1 collagen; P1NP, N-terminal propeptide of type 1 procollagen; N, number of samples; QSP, quantitative systems pharmacology; EM, endometriosis studies

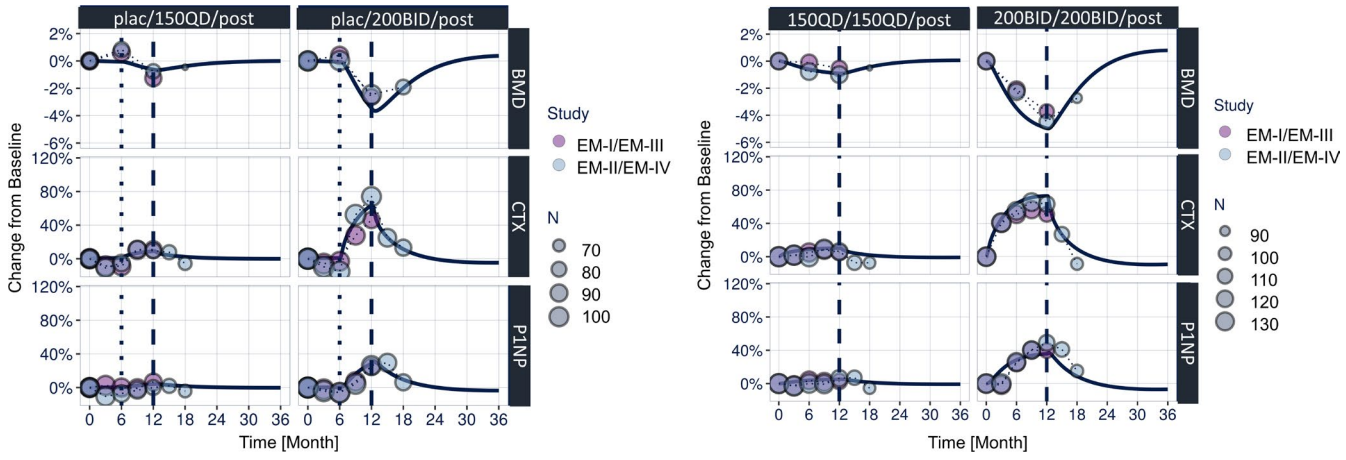

FIGURE 3 Observations and QSP model predictions of BMD and bone turnover biomarker changes during treatment and post-treatment follow-up periods in women treated with elagolix. BMD, CTX, and P1NP observations and model predictions are shown for the four treatment sequences that occurred across the endometriosis clinical studies and their respective extension studies. The left panel shows data for patients receiving placebo (plac) doses in EM-1 or EM-II who continued into their respective extension study (EM-III or EM-IV) and were randomized to receive either 150 mg once daily dose (150 q.d.) or 200 mg twice daily dose (200 b.i.d., e.g., plac/150 q.d./post and plac/200 b.i.d./post). The right panel shows data for patients who received either dosage and remained on the same dose into the extension study (e.g., 150 q.d./150 q.d./post and 200 b.i.d./200 b.i.d./post). Observed values are plotted as circles designated by study and respective extension study in the legend. The number of measurements is denoted by *N* and is represented by the size of the circle. BMD measurements were obtained every 6 months, whereas CTX and P1NP measurements were obtained every 3 months through the 12-month clinical study and for an additional 6 months in the post-treatment follow-up period. The dotted line designates the start of treatment in the left panel, and the dashed line (second) indicates the end of treatment in both panels. See Table 1 for source data and study information. BMD, bone mineral density; CTX, carboxyterminal cross-linked telopeptide of type 1 collagen; P1NP, N-terminal propeptide of type 1 procollagen; QSP, quantitative systems pharmacology; EM, endometriosis studies

model-predicted lumbar spine BMD changes following elagolix treatment up to 24 months with each of the elagolix dosing regimens are summarized in Table 3. The QSP model was used to simulate longer term lumbar spine BMD changes post-treatment of elagolix. Based on the QSP model simulation, median lumbar spine BMD is predicted to return to pre-elagolix treatment or baseline levels within ~ 12 months following a 12-month treatment for both elagolix regimens (Figure 4). The QSP model predictions demonstrate a faster rate of lumbar spine BMD return

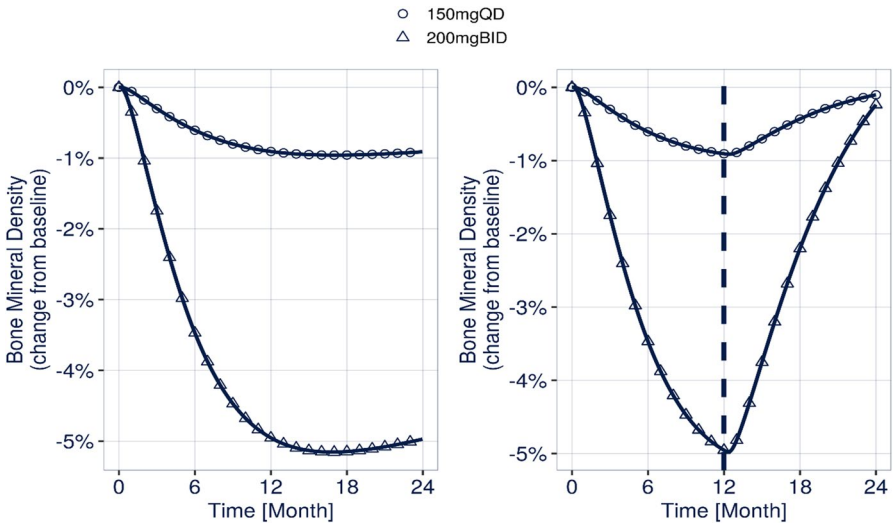

FIGURE 4 QSP model simulations of BMD changes during 12 months of elagolix treatment followed by a 12-month follow-up period. Dashed line indicates the end of elagolix treatment and the beginning of recovery. QSP, quantitative systems pharmacology; BMD, bone mineral density

TABLE 3 Predicted and observed[a] lumbar spine BMD percentage change from baseline with different elagolix regimens

		% Change from baseline (95% CI)			
Regimen	**Study**	**6 Months**	**12 Months**	**18 Months**	**24 Months**
150 mg q.d.	QSP, model	−0.61%	−0.91%	−0.96%	−0.91%
	EM−1/-III[a]	−0.32% (−0.7, 0.07)	−0.63%	NA	NA
	EM-II/-IV[a]	−0.72 (−1.09, −0.35)	−1.10%	NA	NA
200 mg b.i.d.	QSP model	−3.47%	−4.95%	−5.15%	−4.97%
	EM−1/-III[a]	−2.61 (−3.00, −2.22)	−3.6%	NA	NA
	EM-II/-IV[a]	−2.49% (−2.85, −2.13)	−3.91	NA	NA

Note: QSP model predicted values are for continuous dosing up to 24 months.

Abbreviations: BMD, bone mineral density; CI, confidence interval; EM, endometriosis studies; NA, not applicable.

[a]Values obtained from reference 13 for EM-III and EM-IV.

to pretreatment levels for the 200 mg b.i.d. dose that resulted in lower end-of-treatment lumbar spine BMD levels compared with the lower dose at 150 mg q.d. that resulted in less lumbar spine BMD changes (Figure 4).

DISCUSSION

A previously published calcium homeostasis QSP model by Riggs et al.[15,16] with an additional integration of an empirical elagolix dose-E2 model was validated with data from four phase III clinical trials in patients with endometriosis. Model predictions were utilized to inform the appropriate duration of elagolix treatment for the management of endometriosis-associated pain. Without any modifications to the previously published QSP model, the average time course data for lumbar spine BMD and bone biomarkers, CTX and P1NP, were adequately described by the model. To our knowledge, this is the first validation of the model using external data from large phase III clinical trials, including BMD and biomarker data from both on-treatment and PTFU periods. This external validation of the QSP model demonstrated the model robustness for predicting the time course of treatment effects and post-treatment recovery, for both BMD and bone biomarker dynamics. The validated model offers a promising platform for future applications to evaluate the impact of drugs that alter estradiol levels or calcium homeostasis on BMD and bone turnover biomarkers. Some of those applications are discussed below as it relates to the approved elagolix dosing regimens and treatment duration.

Elagolix treatment results in changes in BMD and bone biomarkers through alteration of E2 levels in premenopausal women. By adding an empirical dose-response (dose-E2) model that provides adequate E2 level inputs to the previously developed calcium homeostasis model, a platform was established to enable prediction of BMD and biomarker

changes with elagolix treatment. The direct use of observed E2 levels may lead to erroneous results if not put into context (e.g., diurnal variation and menstrual cycle synchronization). This was addressed in the dose-E2 model development using a weighted nonlinear regression, which accounted for the disparity between the small population and high sampling frequency (e.g., 3 times per week for 3 months, providing significant coverage throughout menstrual cycles) of the phase I study data and the large population and low sampling frequency (e.g., monthly, and initially synchronized with menstrual cycles) of the phase II and III study data. Although this procedure enabled consistent and robust E2 levels, and ultimately QSP model outputs, for the phase II and III observations, it limited the applicability of the model to describing population-level rather than individual-level data. However, describing population trends is often the primary application of QSP models and empirical, less mechanistic models are usually reserved for individual-level predictions.

The QSP model utilized here is based on bone biology and is generally independent of the population being studied, thereby enabling prediction of changes in BMD beyond observed clinical data. However, the simulations generated using the QSP model lack validation of lumbar spine BMD predictions beyond 12 months. Although model predictions enabled extrapolation and hypothesis testing where data were not available, model predictions beyond the range of observed data require future validation with observed clinical data. Such validation using longer term observations may be important to shed light on the possibility of a long-term adaption of the physiological feedback system under continued E2 suppression.[24]

The presented validation of the QSP model demonstrates the value of open-source and transparent QSP models to the MIDD paradigm. This QSP model-based approach was part of the totality of scientific evidence that supported the approved elagolix regimens using also other MIDD approaches, such as the empirical or pharmacometrics-based exposure-response analysis published recently.[25] The exposure-response model enabled prediction of individual patient-level BMD changes as well as characterization of the changes in BMD in patients on placebo. The validated QSP model, on the other hand, enabled simulations of the "what if" scenarios to test various dosing regimens/durations based on the extrapolated change in BMD, a task best approached using mechanistic or physiologically based models.

Simulations using the QSP model demonstrated a plateauing effect of elagolix treatment on lumbar spine BMD over time, with minimal additional reduction in BMD during the second year of treatment. These results are consistent with results obtained from the empirical exposure-response model.[25] Similar trends were also observed with 1 and 2 years of treatment with medroxyprogesterone in women 18–25 years of age, where reductions of 3.5% and 5.7%, respectively, were observed in lumbar spine BMD.[26] Although the magnitude of reduction was lower during the second year of treatment with medroxyprogesterone, the continued reduction may be a characteristic of progesterone-based treatments unlike a GnRH antagonist like elagolix.

Simulated BMD and biomarker changes during the post-treatment period indicated a return to near-baseline levels for both dose levels 6–12 months after stopping elagolix treatment. Such observation reflects the reversible nature of the elagolix-mediated changes in BMD and biomarkers, as well as the faster rate of return to baseline for scenarios with more significant changes at the end of the treatment period. This is consistent with the observed data from the Elaris EM-IV extension study showing faster recovery of BMD in women who were treated with elagolix 200 mg b.i.d. compared to 150 mg q.d.[13] The faster recovery in patients who experience greater changes in BMD during treatment may indicate adaptive feedback mechanisms that trigger larger changes in bone turnover biomarkers in response to larger changes in BMD.

The totality of evidence-based MIDD strategy to support approval of elagolix dosages (150 mg q.d. and 200 mg b.i.d.) in women with moderate to severe pain associated with endometriosis used a previously published QSP bone model by Riggs et al.[15,16] combined with an elagolix dose-E2 model to predict lumbar spine BMD and bone biomarker changes following treatment and post-treatment periods with elagolix. These results demonstrate robust external validation of the QSP model performance compared with the phase III clinical trial data and enabled simulations of various scenarios to support the approved duration of therapy.[3]

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CONFLICT OF INTEREST

All authors are employees of AbbVie Inc. and may hold AbbVie stock and/or stock options.

AUTHOR CONTRIBUTIONS

All authors wrote the manuscript, designed the research, performed the research, and analyzed the data.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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