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ORIGINAL ARTICLE

Interdisciplinary model-informed drug development for extending duration of elagolix treatment in patients with uterine fibroids

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Aim: Elagolix, a gonadotropin-releasing hormone receptor antagonist, was recently approved for heavy menstrual bleeding associated with uterine fibroids (UF, Oriahnn) at a dose of 300 mg twice daily (BID) in combination with add-back therapy (oestradiol 1 mg/norethindrone acetate 0.5 mg [E2/NETA] once daily) for 24 months use. The limited duration of treatment is related to elagolix dose- and duration-dependent decrease in oestrogen that is mechanistically linked to changes in bone mineral density (BMD). The work herein supported the extended treatment duration of 24 months.

Methods: An integrated exposure-response and epidemiological modelling framework of elagolix effects on femoral neck BMD (FN-BMD), informed by real-world data and phase 3 clinical trials data, was developed to predict the time course and magnitude of changes in BMD and its relation to risk of bone fracture in women with UF.

Results: Model results indicated that women treated with elagolix 300 mg BID + E2/NETA in the long term (ie, >24 months) may experience less than 1% loss in FN-BMD per year, relative to placebo. The exposure-response model simulations and clinical risk factors were used to estimate 10-year risk of fractures using the clinically validated Fracture Risk Assessment Tool (FRAX). The impact of elagolix 300 mg BID + E2/NETA treatment on the 10-year risk of hip or major osteoporotic fractures estimated from the FRAX model was minimal compared to that of placebo.

Conclusion: The elagolix integrated exposure-BMD analysis and translation to fracture risk provided an interdisciplinary model-informed drug development framework for clinical benefit-risk evaluation and enabled approval of longer treatment duration to benefit the patient.

KEYWORDS
bone mineral density, elagolix, exposure-response, femoral neck, uterine fibroids

Charlotte Owens Employment at the time author contributed to this work.

1 | INTRODUCTION

Women with symptomatic uterine fibroids (UF), benign hormone-responsive tumours in uterine muscle tissue, can experience heavy periods, lower back pain and additional symptoms that lead to a decrease in their quality of life.[1–4] Treatment options that do not involve invasive surgery, preserve the uterus and preserve fertility are highly desired.[1] Medical therapies have been developed to treat UF symptoms, including gonadotropin-releasing hormone receptor (GnRH) agonists, hormonal birth control methods, progestin-releasing intrauterine devices and some nonhormonal drugs.[4] It has been well established that suppression of oestrogen and progesterone results in fibroid atrophy and decreased morbidity,[4–7] but low oestrogen levels (<10 pg/mL) are associated with bone loss[8,9] and balancing homeostatic hormone regulation in women with oestrogen-dependent diseases has been challenging until the development of GnRH antagonists.[10,11]

Elagolix, an oral, nonpeptide, short-acting GnRH receptor antagonist approved for the management of endometriosis-associated pain and heavy menstrual bleeding (HMB) associated with UF enables dose-dependent suppression of ovarian sex hormones and gonadotropins.[12,13] Like many GnRH therapies, elagolix treatment is associated with hypoestrogenic adverse effects such as hot flushes, headache, nausea, increased serum lipid levels and loss of bone mineral density (BMD). At low doses of elagolix (150 mg once daily [QD]) or at high doses (200 or 300 mg twice daily [BID]) with hormonal add-back therapy (oestradiol 1 mg/norethindrone acetate 0.5 mg QD [E2/NETA]), oestradiol levels can be maintained within the oestradiol therapeutic window of 30-45 pg/mL proposed by Barbieri[8] for preventing bone loss associated with oestrogen-suppressing therapies, while maintaining therapeutic benefits.

Decreased BMD is an important consideration when treating women with hormone modulators that decrease estradiol levels. Low BMD has been linked to higher risk of fractures, especially in elderly women,[14,15] but there are limited reports that describe the longitudinal changes in BMD in adult premenopausal women and the relationship to incident of fractures at postmenopausal age, where the prevalence is high, to BMD loss in this young population of women.[16] Recent studies show that BMD loss can be prevented or restored through hormonal add-back regimens including norethindrone acetate or conjugated equine oestrogens in combination with GnRH therapy,[17–20] while maintaining the efficacy and safety of these combination treatments for various indications and populations.[21]

Among the different anatomical BMD regions, the lumbar spine (LS) is most sensitive to oestrogen suppression-induced bone loss and hence was one of the regions evaluated in support of United States Food and Drug Administration (FDA) approval of elagolix for endometriosis-associated pain and HMB associated with UF.[22,23] The assessment of fracture risk, however, only utilizes BMD changes associated with the femoral neck (FN), the World Health Organization reference standard for the description of osteoporosis,[24] and is therefore the focus of this manuscript. To better understand the relationship between longitudinal changes in BMD in adult premenopausal women and the risk of hip fracture and major osteoporotic fracture (MOF) after menopause, we previously developed a FN-BMD model utilizing real-world data (RWD) and clinical trial data to simulate FN-BMD changes as a function of age.[25] The natural changes in FN-BMD were best described by a bi-exponential model with first-order BMD formation (k_1) and resorption (k_2) rate constants.[25] The output of the FN-BMD model was then translated into the long-term postmenopausal fracture risk of premenopausal women with an epidemiological model, the FRAX tool (https://www.sheffield.ac.uk/FRAX/tool.aspx).[15,26–28] Here, we extend the FN-BMD model in an untreated population to an exposure-response analysis by addition of the response to elagolix treatment via an indirect response model. With this model, the impact of elagolix on FN-BMD changes beyond the observed treatment durations (>12 months) and future bone fracture risk can be assessed for women seeking GnRH medical therapy.

What is already known about this subject

- Suppression of oestrogen due to gonadotropin-releasing hormone receptor modulators results in treatment and duration-dependent increase in bone loss, leading to restricted duration of therapy of useful medical treatments.
- Risk-benefit assessments of bone mineral density changes due to elagolix therapy and the impact on 10-year fracture risk enabled extending treatment duration.

What this study adds

- Women treated with elagolix 300 mg BID + E2/NETA for >24 months may experience <1% loss in femoral neck bone mineral density per year, relative to placebo.
- The impact of elagolix with add-back therapy treatment on the 10-year risk of hip or major osteoporotic fractures was minimal compared to placebo.

2 | METHODS

2.1 | Data sources and participants

The relationship between elagolix exposure and FN-BMD changes was evaluated using data from the Elaris UF phase 3 studies (UF-1, UF-2 and UF-Extend)[29,30] and the Elaris Endometriosis phase 3 studies (EM-1, EM-2, EM-1-Extend and EM-2-Extend).[5,31] Details of these studies have been reported previously.[5,29–31] Briefly, in the UF studies premenopausal women ages 25 to 53 years with HMB associated with UF were randomized 1:1:2 into treatment groups consisting of placebo, elagolix 300 mg BID and elagolix 300 mg BID + E2/NETA. In the endometriosis studies, premenopausal women aged 18-49 years

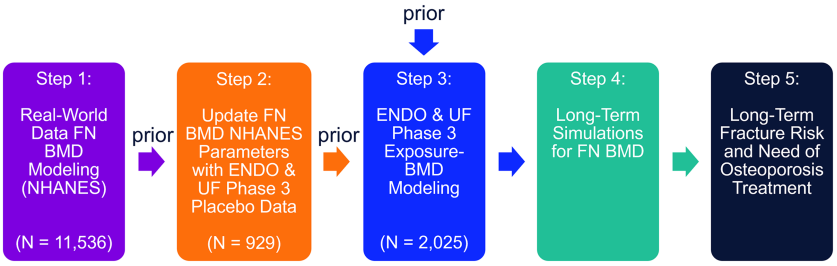

FIGURE 1 Modelling and simulation main concept for femoral neck bone mineral density. BMD, bone mineral density; ENDO, endometriosis; FN, femoral neck; N, number of subjects; NHANES, National Health and Nutrition Examination Survey; UF, uterine fibroids

with endometriosis-associated pain were randomized into dosing groups consisting of placebo and elagolix 150 mg QD and 200 mg BID. UF-1, UF-2, EM-1 and EM-2 were conducted for 6 months with optional extension studies, UF-Extend, EM-1-Extend and EM-2-Extend, for an additional 6 months of treatment consisting of active treatment arms only. For all studies, the FN-BMD was measured with dual energy X-ray (DXA) absorptiometry using Hologic or Lunar machine types and was included in the analysis. Measurements were obtained during the screening period, month 6, month 12 (for those enrolled in the extension study) or premature discontinuation visits during the treatment period, and month 6 and month 12 visits during the post-treatment follow-up (PTFU) period. Data from both endometriosis and UF studies were used to have a broader elagolix exposure range for model development and evaluation, but only the UF results are reported here. All results relating to the endometriosis studies are provided in Supporting Information.

Study protocols were approved by the institutional review boards of the study sites,[29,31] and all the participants gave written informed consent before participation. The studies were conducted according to International Conference on Harmonisation Guidelines for Good Clinical Practice and the ethical principles that have their origin in the Declaration of Helsinki.

2.2 | Modelling of exposure-femoral neck BMD relationship

Exposure-response modelling for changes in FN-BMD in premenopausal women was built using nonlinear mixed-effects modelling in NONMEM 7.4.2 compiled with the GNU Fortran compiler (version 4.8.3). The BMD model parameters were estimated using the first-order conditional (FOCE) estimation method with η-ε INTERACTION.

Exposure-response modelling for FN-BMD was developed in a stepwise manner. First, a bi-exponential model for characterizing the placebo response was developed to describe the natural course of BMD in premenopausal women and this has been published previously (steps 1 and 2 in Figure 1).[25] The placebo model was built utilizing placebo cohort data from the Elaris phase 3 clinical studies (EM-1, EM-2, UF-1 and UF-2).[29,31] A summary of demographics and participants' baseline characteristics is provided in Table 1. In addition to the 6-month placebo BMD data over an age range of 18-53 years from elagolix studies, publicly available RWD from the National Health and Nutrition Examination Survey (NHANES)[32] were used to describe the dynamics of FN-BMD changes over age (a surrogate for time).

Once the model that best described observed FN-BMD changes in the placebo arm was selected,[25] the FN-BMD response to elagolix treatment was added via an indirect response model (step 3 in Figure 1). Priors for model development were generated by re-estimating a previously published exposure-LS-BMD model[23] with FN-BMD data from the Elaris UF studies (UF-1, UF-2 and UF-Extend).[29,30] The population parameter estimates and the variance-covariance matrix of the fixed effects and estimates for the random effects (interindividual variability, IIV) were used as priors. This was achieved by applying the $PRIOR NWPRI option in NONMEM. To have a broader exposure range to more reliably estimate the drug-related parameters, active treatment FN data from the three UF studies consisting of treatment groups of 300 mg BID and 300 mg BID + E2/NETA (N = 700) and four endometriosis studies[5,31] consisting of elagolix treatment groups of 150 mg QD and 200 mg BID (N = 1325) were used to re-estimate all model parameters.

The final exposure-response model conceptualized as an indirect response model described the change from placebo response (PLAC) and assumed a baseline steady state between bone formation and resorption described by the following equations:

$$\frac{dR(t)}{dt} = k_{in} - k_{out} \cdot R(t) \quad (1)$$

$$BMD(t) = PLAC(t) \cdot R(t) \quad (2)$$

and at baseline:

$$R(0) = 1 \text{ and } k_{out} = k_{in}/1 \quad (3)$$

where $dR(t)/dt$ is the change in BMD over time, k_{in} is a zero-order rate constant reflecting bone formation, k_{out} is a first-order rate constant reflecting bone resorption, BMD(t) is the BMD at time t and $R(t)$ is the change in BMD from placebo response (PLAC) at time t. The bi-exponential model for characterizing the placebo response has been published previously[25] and was parameterized in terms of maximum FN-BMD ($PLAC_{max}$) and parameters describing the formation and resorption rate constants in FN-BMD over age (k_1 and k_2), respectively, as follows:

$$PLAC(t) = PLAC_{max} \times \frac{k_1}{k_1 - k_2} \times \left(e^{-k_2 \times \left(AGE + \frac{t}{365}\right)} - e^{-k_1 \times \left(AGE + \frac{t}{365}\right)} \right) \times (1 + fac_{Lunar}) \quad (4)$$

where PLAC(t) is the FN-BMD at time after baseline t in days, $t/365$ is the time since baseline observation time in years and fac_{Lunar} is

TABLE 1 Summary of participant demographic and baseline characteristics

		Patients included in population analysis		
Characteristics		**Endometriosis[a] (N = 1683)**	**Uterine fibroids[a] (N = 790)**	**Total[a] (N = 2473)**
Age (years)	Mean (SD)	32.3 (6.52)	42.4 (5.36)	35.5 (7.76)
	Median	32	43	35
	Min, max	18, 49	25, 53	18, 53
Alcohol use	Never or former	516 (31%)	259 (33%)	775 (32%)
	Current	1162 (69%)	528 (67%)	1690 (68%)
	Missing	5 (0%)	3 (0%)	8 (0%)
Body mass	Mean (SD)	27.6 (6.46)	33.6 (7.25)	29.5 (7.28)
Index (kg/m^2)	Median	26.4	33.0	28.4
	Min, max	16.2, 55.6	18.8, 61.5	16.2, 61.5
Calcium use	No	322 (19%)	762 (96%)	1084 (44%)
	Yes	1361 (81%)	28 (4%)	1389 (56%)
E2 at baseline (pg/mL)	Mean (SD)	79.5 (73.1)	92.8 (81.5)	83.7 (76.1)
	Median	54.2	66.6	57.6
	Min, max	3.24, 624	1.51, 729	1.51, 729
Femoral neck	Mean (SD)	0.302 (0.964)	0.586 (0.885)	0.393 (0.949)
Z-score at	Median	0.210	0.517	0.300
Baseline	Min, max	−1.62, 4.73	−1.43, 4.15	−1.62, 4.73
Machine type	Lunar	950 (56%)	405 (51%)	1355 (55%)
	Hologic	733 (44%)	385 (49%)	1118 (45%)
Race	White	1485 (88%)	232 (29%)	1717 (69%)
	Black	146 (9%)	533 (67%)	679 (27%)
	Asian	16 (1%)	9 (1%)	25 (1%)
	Other	36 (2%)	3 (0%)	39 (2%)
	Missing	0 (0%)	13 (2%)	13 (1%)
Treatment	Placebo[b]	733 (43.55%)	196 (24.81%)	929 (37.57%)
In pivotal	150 mg QD	474 (28.16%)	-	474 (19.17%)
Studies	200 mg BID	476 (28.28%)		476 (19.25%)
	300 mg BID		199 (25.19%)	199 (8.05%)
	300 mg BID + E2/NETA		395 (50.00%)	395 (15.97%)
Tobacco use	Never or former	1290 (77%)	685 (87%)	1975 (80%)
	Current	393 (23%)	104 (13%)	497 (20%)
	Missing	0 (0%)	1 (0%)	1 (0%)
Vitamin D use	No	360 (21%)	718 (91%)	1078 (44%)
	Yes	1323 (79%)	72 (9%)	1395 (56%)

Abbreviations: BID, twice daily; E2, oestradiol; E2/NETA, oestradiol 1.0 mg/norethindrone acetate 0.5 mg once daily; Min, minimum; Max, maximum; QD, once daily; SD, standard deviation.

[a]Data from N = 1325 premenopausal women with endometriosis from the active treatment arms of studies EM-1, EM-2, EM-1-Extend and EM-2-Extend and N = 700 premenopausal women with UF from the active treatment arms of studies UF-1, UF-2 and UF-Extend were included in the exposure-femoral neck BMD analysis.

[b]Patients randomized to placebo treatment arm in pivotal studies EM-1, EM-2, UF-1 and UF-2 were re-randomized to active treatment when entering the optional extension studies UF-Extend, EM-1-Extend and EM-2-Extend.

the factor to account for differences in BMD measured with the Hologic and Lunar machine types.

The effects of elagolix on BMD were modelled using a stimulatory E_{max} function on the bone resorption (k_{out}), as follows:

$$\frac{dR(t)}{dt} = k_{in} - k_{out} \cdot \left(1 + \frac{E_{max} \cdot C_{avg}{}^{HILL}}{EC_{50}{}^{HILL} + C_{avg}{}^{HILL}}\right) \cdot R(t) \quad (5)$$

where E_{max} is the elagolix maximum stimulatory effect on k_{out}, EC_{50} is the elagolix average concentration at which half of the

maximal effect is achieved and HILL is the stimulatory E_{max} curve shape factor. Due to the strong influence of coadministration with E2/NETA on the change in BMD, different population estimates for E_{max} were incorporated into the model. The effect of body mass index (BMI) on bone formation rate (k_{in}) was already included in the base model.[23]

Individual monthly elagolix plasma concentrations (C_{avg}) derived from the final population pharmacokinetic analysis[33] were used in the UF exposure-BMD model. Preliminary exposure-BMD regression analyses demonstrated that elagolix C_{avg} is a better predictor of BMD changes compared to peak or trough concentrations (data not shown).

IIV in BMD parameters and residual variability was modelled using a log-normal random effects model and the proportional error models (see Supporting Information). The BMD model parameters (Equation 5) were estimated using the first-order conditional estimation (FOCE) method with η-ε INTERACTION. Details on the covariate modelling are described in the Supporting Information.

Model evaluations determined the predictive performance of the developed models and examined the usefulness of the models for describing observations. Methods used in model evaluation included goodness-of-fit and visual predictive checks (VPC). For the VPCs, final model parameters were used to simulate 500 replicates of the original data set. Model evaluation was performed by comparing the observed percentages of the predicted median and 95% confidence interval (CI) around the median of percentage change from baseline in FN-BMD at months 6 and 12 in women with UF who received elagolix 300 mg BID + E2/NETA and 300 mg BID. The same analysis was performed for the endometriosis studies (see Supporting Information).

2.3 | FN-BMD simulations beyond the limited duration of clinical trials

Parameter distributions for demographics and baseline characteristics from UF patients (Table 1) were included in the final exposure-FN-BMD model together with the final population pharmacokinetic model for the Elaris UF clinical studies assuming 87.9% dosing compliance as observed in the phase 3 studies[33] to conduct simulations to predict changes in FN-BMD beyond clinical study data (>12 months, step 4 in Figure 1). In addition to the simulations in untreated patients,[25] simulations were generated for continuous treatment with elagolix 300 mg BID + E2/NETA. Each subject with UF was simulated for 8 years, a period that resembles reaching menopausal age (ie, 51 years) depending on the baseline age of the UF population. The final dataset included 1000 virtual UF patients for each scenario and 100 replicates were simulated (total N = 100 000 for each scenario). The median percentage change in BMD was then calculated for each replicate, and the median and 95% CI as well as 95% prediction intervals (PIs) were calculated across the 100 replicates. In addition, the placebo-corrected median and 95% CI for elagolix 300 mg BID + E2/NETA were calculated.

2.4 | Translation of BMD changes to long-term fracture risk in UF patients

The FRAX epidemiologic prediction models have been developed from studying patient-level data from population-based cohorts from Europe, North America, Asia and Australia.[1] The FRAX tool uses country-specific fracture and mortality rates to predict an individual's 10-year probability of MOF (clinical spine, forearm, shoulder or hip) and hip fracture alone based on femoral neck BMD measurement and clinical risk. The FRAX tool provides predictions consistent with observed fracture rates in women and men across multiple countries.[2,3] The 10-year risks of hip fracture and MOF were estimated based on a trajectory of simulated individual FN-BMD values over time beyond the clinical trial period and patient-level fracture risk factors via the FRAX tool for placebo[25] and continuous treatment with elagolix 300 mg BID + E2/NETA for 24 months (step 5 in Figure 1). Longitudinal FN-BMD values for each UF patient were simulated for up to postmenopausal age of 79 years. As the final exposure-BMD model predicts full recovery after end of treatment, a worst-case scenario with no recovery was added. The final dataset included 1000 virtual UF patients for each scenario and 100 replicates were simulated (total N = 100 000 for each scenario), resulting in a BMD value per subject at multiple timepoints (ie, various ages). Risk factors required by the FRAX tool were assumed to be the same across groups. Risk factors such as race, BMI and current smoking status in the UF population were extracted from the simulated virtual population and entered in the FRAX tool. Other fracture risk factors (ie, history of previous fractures, parental history of hip fractures, glucocorticoid use, rheumatoid arthritis and secondary osteoporosis) were not available from the elagolix clinical trials and therefore were considered not present in the FRAX model. Furthermore, although information to define heavy alcohol use (>3 drinks/day) was captured, the majority of the current alcohol users (~98%) reported having <2 drinks/day, and hence were not considered in the FRAX predictions.

The 10-year risk of hip fracture and MOF were estimated for each scenario based on the simulated BMD for Hologic or Lunar machine types at multiple timepoints (ie, various ages) and patient characteristics via the FRAX tool. Based on the simulated patient-level longitudinal data, the age when a particular patient reached the risk-based threshold for anti-osteoporosis treatment was defined as the earliest age when the patient reached a 10-year risk of hip fractures ≥3% or a 10-year risk of MOF ≥20%.[25,34] The median difference in FN-BMD, 10-year risk of hip fractures and MOF, and the proportion of patients reaching the risk-based threshold for anti-osteoporosis treatment between the elagolix-treated populations (with and without recovery) and the untreated population was calculated for each replicate, and the median, 95% CI and 95% PI were calculated across the 100 replicates.

For each comparison, the number needed to "harm" (NNH, where harm = initiation of anti-osteoporosis treatment) was estimated by dividing 1 by the difference in the proportion between treated and untreated population. This NNH can be interpreted as

TABLE 2 Parameter estimates for the final exposure-femoral neck bone mineral density model

Parameter	Population value (θ)		
	Estimate (SEE)	%RSE[a]	95% CI
k_{in} (1/day)	0.00179 (6.54×10^{-05})	3.65	0.00166, 0.00192
BMI on k_{in}[c]	−0.236 (0.117)	49.6	−0.465, −0.00668
E_{max} for elagolix alone	0.0894 (0.00673)	7.53	0.0762, 0.103
E_{max} for elagolix + E2/NETA	0.0291 (0.00458)	15.7	0.0201, 0.0381
Baseline Z-score on E_{max}[e]	0.178 (0.0470)	26.4	0.0859, 0.270
EC_{50} (ng/mL)	92.1 (9.20)	9.99	74.1, 110
Alcohol use on EC_{50}[d]	1.04 (0.319)	30.7	0.415, 1.67
BMI on EC_{50}[c]	1.18 (0.271)	23.0	0.649, 1.71
Age on EC_{50}[c]	1.22 (0.356)	29.2	0.522, 1.92
Hill	3.00 (fix)	...	...
	Interindividual variability (ω^2)		
IIV on EC_{50} (%CV[b])	1.20 (152)	14.0	0.871, 1.53
	Residual variability (σ^2)		
Proportional error	0.000598 (1.29×10^{-05})	2.16	0.000573, 0.000623

Abbreviations: BMI, body mass index; CI, confidence interval; E2/NETA, oestradiol 1.0 mg/norethindrone acetate 0.5 mg once daily; EC_{50}, average concentration at which half of the maximal effect is achieved; E_{max}, maximal effect; IIV, interindividual variability; k_{in}, zero-order rate constant reflecting bone formation; RSE, relative standard error; SEE, standard error of the estimate.

[a]%RSE estimated as the standard error of the estimate divided by the population estimate multiplied by 100.

[b]$\%CV = 100 \times \left(\sqrt{e^{\omega^2} - 1}\right)$.

[c]Continuous covariates, except the baseline Z-score, were normalized to a reference value (median value of the population) and included in the model with a power function: $\left(cov_{i,p}/ref_p\right)^{\theta_{k,p}}$.

[d]Dichotomous categorical covariates were tested multiplicatively to obtain the fractional difference of the parameters between the tested categorical groups: $\left(1 + \theta_{k,q} \times cov_{i,q}\right)$.

[e]The baseline Z-score was tested linearly since negative values can be observed: $(1 + \theta_{k,\mathrm{BLZSCO}} \times (\mathrm{BLZSCO}_i - \mathrm{ref}_{\mathrm{BLZSCO}})$.

the number of patients needed to be treated with elagolix in combination with add-back therapy to result in one additional patient to reach the risk-based threshold for anti-osteoporosis treatment. Figure 1 visualizes the main concept for modelling the exposure-BMD relationship and conducting simulations to predict changes in BMD beyond the observed phase 3 data and up to menopausal age and to evaluate the fracture risk in postmenopausal women via the FRAX tool.

3 | RESULTS

3.1 | Modelling of elagolix impact on FN-BMD

Data from 1325 premenopausal women with endometriosis and 700 premenopausal women with UF from the active treatment arms of elagolix phase 3 clinical trials were included in the exposure-FN-BMD analysis. UF patients were relatively older by a decade, predominately African American and closer to menopause compared to endometriosis patients (Table 1). The final exposure-FN-BMD model was an indirect response model through stimulation of the bone resorption process (k_{out}) with different E_{max} population estimates for coadministration with E2/NETA, a proportional residual error model and IIV on EC_{50}. Patient-specific covariates that were significantly associated with FN-BMD changes due to elagolix treatment included age, BMI, baseline Z-score and baseline alcohol use. The parameter estimates for the final model are listed in Table 2. The model-estimated EC_{50} was 92.1 ng/mL and E_{max} for elagolix dosing with and without add-back therapy were 0.0894 and 0.0291, respectively. The exposure-BMD indirect response model adequately described the central tendency, as well as the variability in the observed FN-BMD data for patients with UF and patients with endometriosis (Supporting Information Figure S3). The model-predicted median percentage change in FN-BMD at 6 and 12 months in women with HMB associated with UF is in the range of the observed bone loss (Figure 2). For the elagolix-treated groups with and without E2/NETA, observed median percentage change in FN-BMD was −0.6% and −2.2% at month 6 and −0.8% and −2.9% at month 12, respectively. Model-predicted median percentage change in FN-BMD was within the 95% CI of the observed values for all treatment groups and timepoints. Results on the effects of significant covariates in the final exposure-BMD model (Supporting Information Figure S4) are described in the Supporting Information.

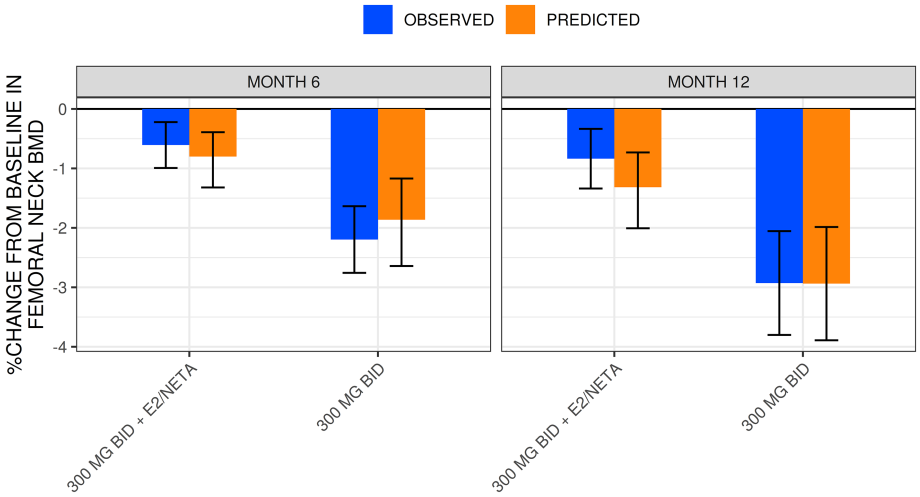

FIGURE 2 Observed and model-predicted bone mineral density loss in phase 3 uterine fibroid clinical trials. Observed and model-predicted percentage change from baseline in femoral neck bone mineral density (BMD) for continuous treatment of elagolix 300 mg twice daily (BID) dosing with and without add-back therapy (oestradiol 1 mg/norethindrone acetate 0.5 mg once daily [QD] (E2/NETA]) are shown for months 6 and 12. Median (bar plots), 2.5th and 97.5th percentiles around the median (error bars) of the predicted percentage change from baseline are compared with the observed data

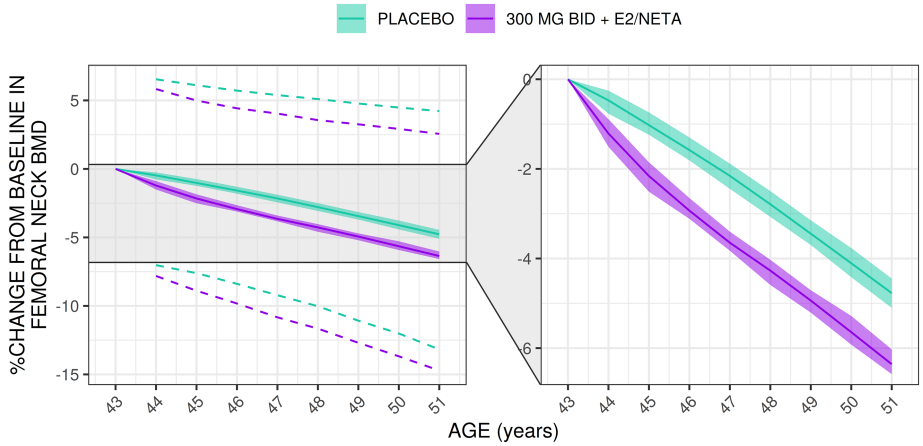

FIGURE 3 Simulated percentage change from baseline in femoral neck bone mineral density over time up to menopausal age for uterine fibroid patients. Simulated percentage change from baseline in femoral neck bone mineral density (BMD) from median age of 43 up to menopausal age of 51 for uterine fibroid patients. Simulations assume continuous treatment of placebo or elagolix 300 mg twice daily (BID) with oestradiol 1 mg/norethindrone acetate (E2/NETA) 0.5 mg once daily (QD) dosing. Lines and shaded regions represent the median and 95% confidence interval of the median. Dashed lines represent the 95% prediction interval

3.2 | Model simulations of elagolix impact on longitudinal FN-BMD

The final exposure-BMD model and population pharmacokinetic model,[33] together with the characteristics of the patient populations in elagolix phase 3 clinical trials, were used to conduct simulations to predict a trajectory of individual changes in FN-BMD for placebo and continuous elagolix treatment (300 mg BID + E2/NETA) groups beyond the clinical trial period (6-12 months). Simulations of elagolix 300 mg BID + E2/NETA continuous dosing over 8 years, a period that resembles reaching menopausal age relative to the median age of this patient population, suggest that the predicted median percentage change from baseline BMD at 24 months is −2.2% (lower bound of 95% CI of −2.5%) (Figure 3), compared to −1.0% (lower bound of 95% CI of −1.2%) in the placebo group.

3.3 | Prediction of elagolix impact on long-term postmenopausal fracture risk in women with uterine fibroids

The FRAX tool was employed to extend the BMD model projections to clinically relevant predictions of future fracture risk. When accounting for the recovery in FN-BMD post elagolix 300 mg BID + E2/NETA, the difference in 10-year risk of hip and major osteoporosis fractures between the elagolix-treated and untreated (ie, placebo) populations was less than 0.01% (Figure 4B). The median age of UF patients receiving 24-month elagolix BID + E2/NETA treatment reaching the risk-based threshold for anti-osteoporosis treatment was the same as for untreated patients (age 72 years; Figure 4B). The difference in the proportion of patients reaching the risk-based threshold for anti-osteoporosis treatment

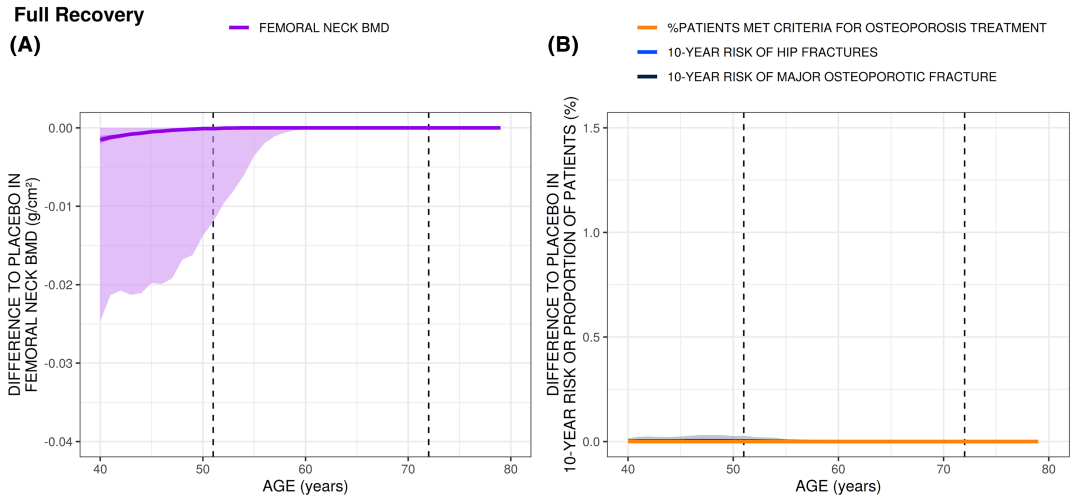

FIGURE 4 Predicted 10-year risk of hip and major osteoporotic fractures and proportion of uterine fibroids patients in need of osteoporosis treatment up to postmenopausal age assuming full recovery. Simulated outcomes of difference to placebo in bone mineral density (BMD), predicted 10-year risk of hip and major osteoporotic fractures (MOF) and calculated proportion of patients in need of osteoporosis treatment up to postmenopausal age following 24-month elagolix treatment (300 mg twice daily [BID] with oestradiol 1 mg/norethindrone acetate 0.5 mg once daily [QD]) in uterine fibroid patients. Simulations were performed assuming full recovery in BMD loss following elagolix treatment. Lines and shaded regions represent predicted median and 95% prediction interval of the median for femoral neck BMD (A), 10-year risk of hip fractures, MOF and proportion of patients in need of osteoporosis treatment (B). The dashed vertical lines represent the median age when a typical UF patient may reach menopause (ie, 51 years) and the estimated median age when UF patients were recommended to initiate osteoporosis treatment (ie, 72 years)

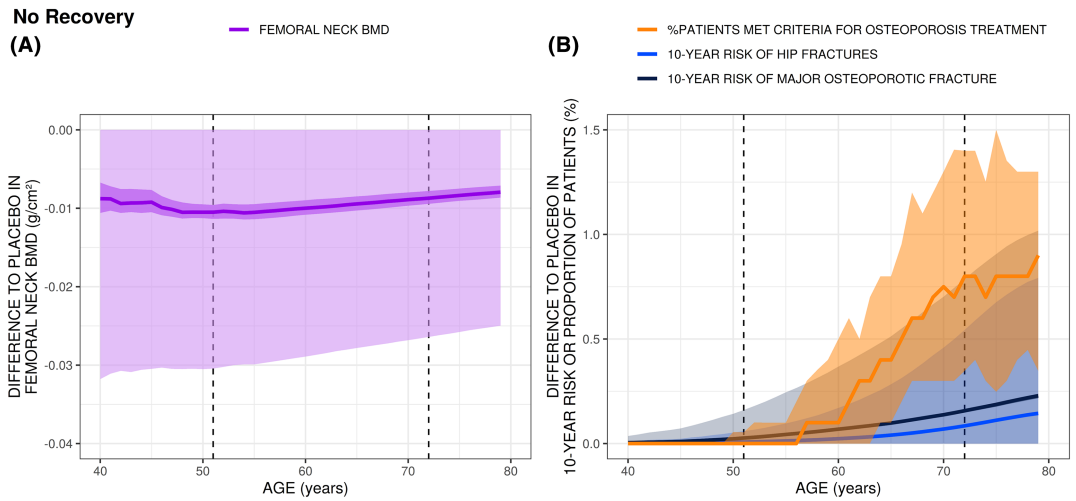

FIGURE 5 Predicted 10-year risk of hip and major osteoporotic fractures and proportion of uterine fibroids patients in need of osteoporosis treatment up to postmenopausal age assuming no recovery. Simulated outcomes of difference to placebo in bone mineral density (BMD), predicted 10-year risk of hip and major osteoporotic fractures (MOF), and calculated proportion of patients in need of osteoporosis treatment up to postmenopausal age following 24-month elagolix treatment (300 mg twice daily [BID] with oestradiol 1 mg/norethindrone acetate 0.5 mg once daily [QD]) in uterine fibroid patients. Simulations were performed assuming no recovery in BMD loss following elagolix treatment. Lines and shaded regions represent predicted median and 95% prediction interval of the median for femoral neck BMD (A), 10-year risk of hip fractures, MOF and proportion of patients in need of osteoporosis treatment (B). The dashed vertical lines represent the median age when a typical UF patient may reach menopause (ie, 51 years) and the estimated median age when UF patients were recommended to initiate osteoporosis treatment (ie, 72 years)

between the untreated and treated groups was extremely small (less than 0.01%; Figure 4B).

Without considering recovery in FN-BMD post-elagolix 300 mg BID + E2/NETA, such risk differences increased as age increased, although the differences were still small. For example, at age 72, premenopausal women who received elagolix 300 mg BID + E2/NETA for 24 months had an increase of 0.08% in 10-year risk of hip fractures compared to placebo (Figure 5B). These women also had an

increase of 0.2% in 10-year risk of MOF compared to the placebo group (Figure 5B). The differences in the proportion of patients reaching the risk-based threshold for anti-osteoporosis treatment between the treated group without recovery and the placebo group also increased as age increased, although the differences were small (Figure 5B). An additional 0.8% of patients who received premenopausal elagolix 300 mg BID + E2/NETA treatment for 24 months reached the risk-based threshold for anti-osteoporosis treatment at age 72, compared to placebo. Therefore, without considering the post-treatment recovery in FN-BMD, 125 patients (ie, NNH) needed to be treated with elagolix 300 mg BID + E2/NETA for 24 months to cause one additional patient to reach the risk-based threshold for initiating anti-osteoporosis treatment at age 72. Supporting Information Table S1 summarizes the impact of elagolix 300 mg BID + E2/NETA 1/0.5 mg QD treatment on the initiation of anti-osteoporosis treatment at ages 45, 55, 65 and 75 years.

4 | DISCUSSION

Real-world data provide valuable information to describe the natural history of physiological and pathophysiological events. In the case of BMD changes, it offers an opportunity to contextualize the long-term safety profile in a patient population when BMD loss is induced by medical therapies such as chronic corticosteroids, chronic proton pump inhibitors, GnRH agonists and antagonists, and injectable progestin-only contraceptives. To inform regulatory decision making with evidence beyond the observed clinical trial data, conducting a quantitative evaluation becomes an essential part of the benefit-risk evaluation for such therapies.

To understand the natural history of BMD in premenopausal women and mitigate the need for long observational studies, publicly available RWD from NHANES database and clinical trial data from placebo cohorts consisting of women with endometriosis or uterine fibroids were combined and analysed. Both data sources were utilized in previous work to describe the dynamics of FN-BMD natural changes due to aging to enable simulations of longitudinal BMD changes over durations beyond the length of phase 3 clinical trials.[25] For clinical relevance and to contextualize the BMD simulation results, an epidemiological model was employed to translate the simulated BMD changes into a long-term postmenopausal fracture risk. This prior work provided the framework for extending this model to understand BMD loss induced by medical therapies such as elagolix.

Previous assessments of BMD loss due to oestrogen-suppressing medical therapies have been reported,[29,35,36] but the natural BMD changes could not be differentiated from medically induced changes in BMD. The culmination of this work with the preceding foundational work[25] would have required decades of observations and clinical measurements to generate an accurate benefit-risk assessment for patients. To our knowledge, this is the first report that quantifies longitudinal adverse changes in FN-BMD in premenopausal women caused by medical treatments using integrated modelling, RWD and clinical trials data, with further translation to clinically relevant predictions of fracture risk. Conceptually, a similar framework linking the disciplines of pharmacology and disease epidemiology into a quantitative framework was previously implemented for the neuraminidase inhibitor oseltamivir for the treatment of influenza by Kamal et al.[37]

The Bateman function was the basis for the development of the exposure-response model for FN-BMD changes associated with elagolix treatment reported here. Exposure-BMD modelling using data from three UF and four endometriosis phase 3 studies revealed an exposure-response relationship between elagolix average plasma concentrations and changes in FN-BMD. This relationship was conceptualized as an indirect response model with zero-order bone formation and first-order bone resorption rates.

The estimated EC_{50} of 92.1 ng/mL is slightly lower than the predicted exposure with 300 mg BID dosing (median C_{avg} concentration of 189 ng/mL with 5th and 95th percentiles of 97.2 and 391 ng/mL).[33] The model-predicted median percentage change in FN-BMD for placebo (at month 6) and elagolix 300 mg BID + E2/NETA (at months 6 and 12) is consistent with the observed bone loss. The E_{max} for elagolix 300 mg BID monotherapy is estimated to be 3.1-fold higher relative to coadministration with E2/NETA. Such a difference is reflected in the small BMD change with 300 mg BID + E2/NETA regimen (∼−1% BMD change from baseline after 12 months). Simulations of elagolix 300 mg BID + E2/NETA suggest that the predicted median percentage change from baseline FN-BMD at 24 months is −2.2% (lower bound of 95% CI of −2.5%). These results suggest that clinically relevant FN-BMD changes may not be expected in most women with the approved dosage of elagolix 300 mg BID + E2/NETA 1/0.5 mg QD for 24 months (<1% placebo-corrected loss in FN-BMD per year would be expected).

The impact of premenopausal elagolix 300 mg BID + E2/NETA treatment on postmenopausal, long-term bone health and outcomes, utilizing simulated UF patient populations and the FRAX tool, demonstrated that the 10-year risk of fractures was minimal for elagolix with hormonal add-back treatment, especially if considering the natural recovery in FN-BMD post-elagolix treatment.[30] Exposing women to elagolix during premenopausal age also did not result in an earlier initiation of anti-osteoporosis treatment when comparing predictions based on clinical trial data in untreated and treated UF populations. Based on the NNH analysis, an extremely large number (100 000 or more) of patients needed to be treated with elagolix 300 mg BID + E2/NETA to cause one additional patient to reach the risk-based threshold for anti-osteoporosis treatment when the natural recovery in FN-BMD was taken into consideration. In the worst-case scenario, assuming no recovery in FN-BMD, the NNH was 125 at the age of 72 years. For comparison, the NNH for renal insufficiency in patients undergoing intensive blood pressure control is 50.[38] With respect to statin use over 5 years, the NNH for diabetes is estimated between 125 and 250.[39] Although this worst-case scenario was evaluated, the UF phase 3 clinical trials demonstrated post-treatment recovery in FN-BMD in both the elagolix monotherapy and in combination with E2/NETA.[30]

These simulation results provide clinicians and other stakeholders with additional quantitative evidence about the benefit-risk profile of

elagolix in UF patients, which can help guide clinical and economic decision making regarding elagolix 300 mg BID + E2/NETA 1/0.5 mg QD treatment for women with UF. One of the limitations in this approach is related to an assumption that the clinical risk factors in the UF patient population (ie, race, BMI and current smoking status) from elagolix phase 3 trials used for the FRAX calculation of 10-year risk of fractures is reflective of the entire patient population. This assumption is reasonable given that the phase 3 trial populations were UF patients that are expected to reflect the targeted patient population in the real world.

Another limitation is related to the effect of different reference ranges in BMD on the diagnosis of osteoporosis. Calculation of T-scores should ideally be based on peak BMD levels and standard deviations using ethnicity-specific reference ranges. The FRAX calculation for 10-year risk of major osteoporotic fracture for black women is less than half that for white women with identical risk factors,[40] which could potentially delay intervention with osteoporosis therapy. Despite the limitations, the FRAX tool provides a quantitative estimation of fracture risk, especially considering that the difference in 10-year risk between untreated (ie, placebo) and treated populations was used herein to extend the BMD model projections to clinically relevant predictions of future fracture risk.

In conclusion, results from these analyses highlighted key elagolix exposure-safety relationships and supported the approval of elagolix 300 mg BID + E2/NETA 1/0.5 mg QD for a treatment duration of 24 months for the management of HMB associated with UF. The combined utility of RWD and exposure-response modelling to quantitatively describe the BMD trajectory in premenopausal women beyond the limited clinical trials data, and to assess long-term postmenopausal fracture risk, highlights the importance of collaboration among various quantitative disciplines within drug development in assessing the benefit-risk of new medical treatments. In the case of elagolix with low-dose hormonal add-back therapy, this work enabled approval of longer treatment duration to benefit the patient.

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COMPETING INTERESTS

D.B., I.W., N.M.M., S.E.C. and M.S. are employees of AbbVie and may hold AbbVie stock or stock options. C.O. is a former AbbVie employee and may hold stock or stock options. W.G. is an employee of Analysis Group, Inc., which has received consulting fees from AbbVie.

CONTRIBUTIORS

D.B., I.W. and M.S. wrote the manuscript. D.B., I.W., N.M.M, S.E.C, C.O. and M.S. designed the research. D.B., I.W. and M.S. performed the research. D.B. and W.G. analysed the data. All authors participated in the revising of the manuscript.

CONSENT TO PARTICIPATE

All participants provided written consent prior to participation or study-related procedures.

CONSENT FOR PUBLICATION

All individual participants signed informed consent regarding publishing their data.

TRIAL REGISTRATION

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DATA AVAILABILITY STATEMENT

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual and trial-level data (analysis data sets), as well as other information (eg, protocols and Clinical Study Reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. This clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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