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ARTICLE

Integrating real-world data and modeling to project changes in femoral neck bone mineral density and fracture risk in premenopausal women

Denise Beck[1] | **Insa Winzenborg**[1] | **Wei Gao**[2] | **Nael M. Mostafa**[3] | **Peter Noertersheuser**[1] | **Stephanie E. Chiuve**[4] | **Charlotte Owens**[5] | **Mohamad Shebley**[3]

[1]Clinical Pharmacology and Pharmacometrics, AbbVie Deutschland GmbH & Co. KG, Ludwigshafen am Rhein, Germany

[2]Analysis Group, Boston, Massachusetts, USA

[3]Clinical Pharmacology and Pharmacometrics, AbbVie, North Chicago, Illinois, USA

[4]Global Epidemiology, AbbVie, North Chicago, Illinois, USA

[5]Clinical Development, General Medicine, AbbVie, North Chicago, Illinois, USA

Correspondence
Mohamad Shebley, Clinical Pharmacology and Pharmacometrics, AbbVie, 1 North Waukegan Road, Bldg. AP31-3, North Chicago, IL 60064, USA.
Email: mohamad.shebley@abbvie.com

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Abstract

Decline of bone mineral density (BMD) during menopause is related to increased risk of fractures in postmenopausal women, however, this relationship in premenopausal women has not been established. To quantify this relationship, real-world data (RWD) from the National Health and Nutrition Examination Survey (NHANES), and longitudinal data from the elagolix phase III clinical trials were modeled across a wide age range, and covariates were evaluated. The natural changes in femoral neck BMD (FN-BMD) were well-described by a bi-exponential relationship with first-order BMD formation (k_1) and resorption (k_2) rate constants. Body mass index (BMI) and race (i.e., Black) were significant predictors indicating that patients with high BMI or Black race experience a relatively lower BMD loss. Simulations suggest that untreated premenopausal women with uterine fibroids (UFs) from elagolix phase III clinical trials (median age 43 years [minimum 25–maximum 53]) lose 0.6% FN-BMD each year up to menopausal age. For clinical relevance, the epidemiological FRAX model was informed by the simulation results to predict the 10-year risk of major osteoporotic fracture (MOF). Premenopausal women with UFs, who received placebo only in the elagolix phase III trials, have a projected FN-BMD of 0.975 g/cm^2 at menopause, associated with a 10-year risk of MOF of 2.3%. Integration of modeling, RWD, and clinical trials data provides a quantitative framework for projecting long-term postmenopausal risk of fractures, based on natural history of BMD changes in premenopausal women. This framework enables quantitative evaluation of the future risk of MOF for women receiving medical therapies (i.e., GnRH modulators) that adversely affect BMD.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Changes in bone mineral density (BMD) in women due to estrogen decline during menopause and its relationship to the increased risk of bone fractures are well-established.

Trial registration: ClinicalTrials.gov identifiers: NCT01620528 (EM-1), NCT01931670 (EM-2), NCT02654054 (UF-1), and NCT02691494 (UF-2).

WHAT QUESTION DID THIS STUDY ADDRESS?

What is the magnitude of longitudinal natural change in BMD in untreated premenopausal women and its relationship to the 10-year fracture risk?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This study quantified the magnitude of longitudinal natural decline in femoral neck BMD in premenopausal women across healthy and patient populations and its translation to long-term postmenopausal fracture risk, using real-world data (RWD) and clinical trials data coupled with modeling and simulation.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

This study provides a model-informed drug development (MIDD) approach that integrates RWD and clinical trials data to evaluate bone health quantitatively and longitudinally in premenopausal women. Our MIDD approach enables prediction of the magnitude of change in BMD and fracture risk due to medical treatments over time to inform the risk-benefit evaluation of new therapies.

INTRODUCTION

The risk of bone fractures due to low bone mineral density (BMD) in premenopausal women is rare.[1] On the other hand, the prevalence is higher in postmenopausal women, where the low estrogen levels after menopause lead to increased bone resorption, low BMD, and higher risk for fractures.[2] Although a plethora of literature is available on the longitudinal BMD changes associated with fracture risk in postmenopausal women, there are limited reports that describe the longitudinal changes in BMD in adult premenopausal women, and scarcely at all in women treated with therapies that are associated with BMD loss (e.g., chronic corticosteroids, chronic proton pump inhibitors, GnRH agonists and antagonists, injectable progestin-only contraceptives, etc.).[3]

Quantitative understanding of the time course of BMD changes in this population is valuable to evaluate the potential risk of bone fractures in premenopausal women who require medical treatments associated with BMD loss, primarily because routine BMD screening in healthy premenopausal women is not recommended, due to the lack of data relating incident fractures to BMD loss in this population of women.[4] In addition, BMD changes are monitored in some randomized clinical trials over limited durations (i.e., 6–12 months), and, therefore, the impact of placebo or treatment on BMD changes beyond the clinical trial period is limited, hindering a quantitative understanding of long-term effects on BMD. As a result, restricted duration of therapeutic use of new and promising medical treatments is imposed upon approval of these therapies as a precaution to prevent increasing the risk for bone fractures.[5–7]

As a bone fracture has substantial personal and economic costs, risk assessment tools have been developed in recent years in order to identify those at high risk for bone fracture. Most notably, the FRAX tool[8] developed by the University of Sheffield using nine cohort's primary data from patient populations in North America, Europe, Latin America, Asia, and Australia. This epidemiologic-based model used BMD at the femoral neck (FN) and other clinical risk factors as input in order to predict 10-year risk of bone fractures. The FRAX tool has been validated with extensive data from multiple cohorts and widely used in various studies.[9]

Real-world data (RWD) have recently attracted attention by regulatory agencies as an additional approach to generate evidence in support of drug approvals.[10] In the current work, RWD from the National Health and Nutrition Examination Survey (NHANES) that summarized FN-BMD results in pre- and postmenopausal women,[11] combined with BMD data from elagolix phase III clinical trials in patients with endometriosis or uterine fibroids (UFs) who received placebo for a limited duration, were integrated to develop a modeling and simulation framework that describes longitudinal changes in BMD.

METHODS

Data sources and participants

The FN-BMD analysis included data from four multicenter, double-blind, placebo-controlled, randomized studies in premenopausal 18 to 49-year-old women with moderate to severe endometriosis-associated pain (EM-1[12] and EM-2[13]) and in premenopausal 25 to 53-year-old women with heavy menstrual bleeding (HMB) associated with UFs (UF-1[14] and UF-2[15]). These clinical trials were selected because elagolix has been approved as a medical treatment for endometriosis and to manage HMB associated with UFs in premenopausal women. The clinical trials consisted of a 6-month treatment

period and a post-treatment follow-up (PTFU) period of up to 12 months (if applicable). Study protocols were approved by the institutional review boards of the study sites, and all the participants gave written informed consent before participation. The studies were conducted according to the International Conference on Harmonization Guidelines for Good Clinical Practice and the ethical principles that have their origin in the Declaration of Helsinki.[16,17]

Because elagolix studies collected FN-BMD measurements over a limited age range (18–53 years), NHANES data[11] over a wide range of age (≥8 years old up to postmenopausal age) were utilized to describe the dynamics of FN-BMD over age in pre- and postmenopausal women prior to incorporating the elagolix studies EM-1 and EM-2 in women with endometriosis and studies UF-1 and UF-2 in women with UFs in the FN-BMD analysis.

The NHANES survey examined a nationally representative sample of about 5000 persons each year. The NHANES interview included demographic, socioeconomic, dietary, and health-related questions. The physical examinations consisted of medical, dental, and physiological measurements, as well as laboratory tests. More information about the survey and the publically available results can be found on the NHANES website.[11]

Dual energy X-ray absorptiometry of FN-BMD

For each subject in the four clinical studies, the FN-BMD during the screening period, at the month 6 or premature discontinuation visits during the treatment period, and at the month 6 and the month 12 visits during the PTFU period were measured with the dual energy x-ray absorptiometry (DXA) using Hologic or Lunar machine type. For the analyses of changes in BMD in women with UFs and women with endometriosis, BMD data from $N = 929$ patients following placebo treatment from studies EM-1, EM-2, UF-1, and UF-2 were included.

The NHANES examination components included one FN-BMD measurement from each of the untreated women ($N = 11{,}536$) measured with DXA scans using Hologic machine type.[18–21]

Modeling of age and FN-BMD relationship

In order to extend the understanding of the natural time course of BMD changes in premenopausal women, FN-BMD data over a wide range of ages (≥8 years old up to postmenopausal age) was used from NHANES data. As a first step, a bi-exponential model was fitted to the NHANES BMD data to describe the dynamics of FN-BMD over the studied baseline age range. A nonlinear least squares estimation approach with R[22] (version 3.5.1) using the "nls()" function was conducted to characterize the relationship between age as a predictor variable and the FN-BMD. The bi-exponential model was parameterized in terms of maximum FN-BMD (FN_{max}) and parameters describing the formation and resorption rate constants in FN-BMD over age (k_1 and k_2), respectively, as follows:

$$FN\,(AGE) = FN_{max} \times \frac{k_1}{k_1 - k_2} \times \left(e^{-k_2 \times AGE} - e^{-k_1 \times AGE}\right). \quad (1)$$

The population parameter estimates and the variance-covariance matrix of the fixed effects of the NHANES-based model was used as a prior to inform the next step of modeling FN-BMD using the phase III clinical trials data. This was achieved by applying the $PRIOR NWPRI option in NONMEM.

The placebo BMD data from two studies in women with UFs and two studies in women with endometriosis were then used to re-estimate all model parameters by applying the following extension of Equation 1 in order to include the dynamics over time and to account for each type of DXA scan machine (Hologic and Lunar):

$$FN(t) = FN_{max} \times \frac{k_1}{k_1 - k_2} \times \left(e^{-k_2 \times \left(AGE + \frac{t}{365}\right)} - e^{-k_1 \times \left(AGE + \frac{t}{365}\right)}\right) \times \left(1 + fac_{Lunar}\right) \quad (2)$$

where FN(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 the factor to account for differences in BMD measured with Hologic and Lunar machine types. Parameter estimation results from the NHANES-only model were used as prior information in this estimation step.

Interindividual variability (IIV) in BMD parameters and residual variability was modeled using a log-normal random effects model and the proportional error models (Supplementary Methods). The FN-BMD model utilizing clinical trials data was a nonlinear mixed effect model built in NONMEM version 7.4.2 using the first-order conditional estimation (FOCE) method with η-ε INTERACTION. Details on the covariate modeling are described in the Supplementary Methods.

Model selection for interim and final models was performed based on estimation of physiologically reasonable, precise, and statistically significant parameter estimates (95% confidence intervals [CIs] do not include reference values). In addition, the likelihood ratio test was used for hypothesis testing to discriminate among alternative nested models. All statistical tests were conducted at the 0.01 significance level, except tests in the backward elimination step of the covariate selection procedure that were conducted at the 0.001 significance level.

Model evaluation included goodness-of-fit plots and visual predictive checks (VPCs). 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 and predicted median and 95% CI of percentage change from baseline in FN-BMD over time.

FN-BMD simulations beyond the limited duration of clinical trials

Parameter distributions for demographics and baseline characteristics from patients with UFs (Table 1) were included in the final model, and simulations to predict FN-BMD beyond the clinical trial period were conducted. Each subject with UF was simulated for 8 years, a period that resembles reaching menopausal age (i.e., 51 years) depending on the baseline age of the UF population. The final data set included 1000 virtual patients and 100 replicates were simulated (total $N = 100{,}000$). The median FN-BMD, percentage change from baseline in FN-BMD and Z-score was then calculated for each replicate, and the median and 95% CIs as well as 95% prediction intervals (PIs) were calculated across the 100 replicates. Details on additional simulations

TABLE 1 Summary of participant demographic and baseline characteristics

Characteristics		NHANES[a] ($N = 11{,}536$)	Patients included in population analysis		
			Endometriosis[b] ($N = 1683$)	UFs[b] ($N = 790$)	Total[b] ($N = 2473$)
Age, years	Mean (SD)	41.4 (22.4)	32.3 (6.52)	42.4 (5.36)	35.5 (7.76)
	Median	43	32	43	35
	Min–max	8–85	18–49	25–53	18–53
Alcohol use	Never or former	5135 (45%)	516 (31%)	259 (33%)	775 (32%)
	Current	1522 (13%)	1162 (69%)	528 (67%)	1690 (68%)
	Missing	4879 (42%)	5 (0%)	3 (0%)	8 (0%)
BMI, kg/m^2	Mean (SD)	27.3 (7.05)	27.6 (6.46)	33.6 (7.25)	29.5 (7.28)
	Median	26.4	26.4	33.0	28.4
	Min–max	12.4–65.5	16.2–55.6	18.8–61.5	16.2–61.5
Calcium use[c]	No	7168 (62%)	322 (19%)	762 (96%)	1084 (44%)
	Yes	4368 (38%)	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
FN *Z*-score at baseline	Mean (SD)	-	0.302 (0.964)	0.586 (0.885)	0.393 (0.949)
	Median	-	0.210	0.517	0.300
	Min–max	-	−1.62 to 4.73	−1.43 to 4.15	−1.62 to 4.73
Machine type	Lunar	0 (0%)	950 (56%)	405 (51%)	1355 (55%)
	Hologic	11,536 (100%)	733 (44%)	385 (49%)	1118 (45%)
Race	White	4923 (43%)	1485 (88%)	232 (29%)	1717 (69%)
	Black	2488 (22%)	146 (9%)	533 (67%)	679 (27%)
	Asian	0 (0%)	16 (1%)	9 (1%)	25 (1%)
	Other	4125 (35%)	36 (2%)	3 (0%)	39 (2%)
	Missing	0 (0%)	0 (0%)	13 (2%)	13 (1%)
Tobacco use	Never or former	1690 (15%)	1290 (77%)	685 (87%)	1975 (80%)
	Current	8064 (70%)	393 (23%)	104 (13%)	497 (20%)
	Missing	1782 (15%)	0 (0%)	1 (0%)	1 (0%)
Vitamin D use[c]	No	7539 (65%)	360 (21%)	718 (91%)	1078 (44%)
	Yes	3997 (35%)	1323 (79%)	72 (9%)	1395 (56%)

Abbreviations: BMI, body mass index; E2, estradiol; FN, femoral neck; Min, minimum; Max, maximum; NHANES, National Health and Nutrition Examination Survey; UFs, uterine fibroids.

[a]Data from: Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey [https://www.cdc.gov/nchs/nhanes/] [updated January 7, 2019; cited March 6, 2019].

[b]Data from $N = 733$ premenopausal women with endometriosis from the placebo arms of studies EM-1 and EM-2 and $N = 196$ premenopausal women with UFs from the placebo arms of studies UF-1 and UF-2 were included in the FN-bone mineral density analysis.

[c]Subjects that participated in EM-1 and EM-2 were instructed to take 400 IU vitamin D, along with 500 to 1000 mg of calcium daily during the 6-month treatment period.[17]

that were conducted for the endometriosis and a combined population are described in Supplementary Methods.

Translation of BMD changes to long-term fracture risk in patients with UFs

The FRAX tool was previously developed based on baseline and follow-up data of clinical risk factors known to be correlated to hip and major osteoporotic fractures, from nine prospective population-based cohorts. FN-BMD was used as a continuous variable in the analysis to compute the probability of fracture risk.[23]

Using the final model, a trajectory of individual BMD values over time beyond the clinical trial period was simulated. Each untreated subject with UFs was simulated for up to postmenopausal age of 79 years. The final data set included 1000 virtual patients for each subpopulation, and 100 replicates were simulated (total $N = 100{,}000$), ending with a BMD value per subject at multiple timepoints (i.e., various ages). FRAX requires patient-level fracture risk factors and BMD value as input to predict future risk using risk factors described in the Supplementary Methods.

The 10-year risk of hip and major osteoporotic fractures (MOFs) were estimated based on the simulated BMD at multiple timepoints (i.e., various ages) and patient characteristics via the FRAX tool. For example, a subject at premenopausal age of 43 years with the respective predicted baseline BMD was simulated at different ages up to postmenopausal age of 79 years and for each age the simulated BMD value was entered into the FRAX tool.

The proportion of women who reached the risk-based threshold recommended to initiate osteoporosis treatment was determined by comparing estimated 10-year risk of fractures to corresponding thresholds (10-year risk of hip fractures ≥3% or 10-year risk of MOF ≥20%).[24] The age when osteoporosis treatment was recommended to initiate and the proportion of patients in need of osteoporosis treatment were estimated. The median FN-BMD, 10-year risk of hip fractures and MOFs and proportion of patients in need of osteoporosis treatment was then calculated for each replicate, and the median, 95% CIs and 95% PIs were calculated across the 100 replicates.

Figure S1 visualizes the main concept for modeling FN-BMD and conducting simulations to predict changes in BMD beyond the observed phase III data and up to menopausal age, and to evaluate the fracture risk in postmenopausal women via the FRAX tool.

RESULTS

Data from 11,536 untreated women from the NHANES database, 733 premenopausal women diagnosed with endometriosis,[17] and 196 premenopausal women diagnosed with UFs[16] from the placebo arms of elagolix phase III clinical trials, and the associated subject demographics and baseline characteristics are summarized in Table 1. The overall baseline demographics were similar across population data sets, except for age (median: 43 years [minimum 8 – maximum 85 years) for NHANES compared with 32 years (18–49 years) for endometriosis patients and 43 years (25–53 years) for patients with UFs), body mass index (BMI; median: 26.4 [minimum 12.4 – maximum 65.5] for NHANES compared with 26.4 [16.2–55.6] for patients with endometriosis and 33.0 [18.8–61.5] for patients with UFs), and race (White or Asian or other or missing vs. Black: 78% vs. 22% for NHANES compared with 91% vs. 9% for patients with endometriosis and 33% vs. 67% for patients with UFs).

The NHANES questionnaire components on reproductive health from 2005 to 2006 captured whether women are suffering from common gynecological disorders. There were 2.8% and 4.6% of the women who were diagnosed with endometriosis and UF, respectively, indicating that the NHANES RWD is reflective of the targeted patient populations for elagolix trials.

NHANES data consisted of one BMD assessment record per individual, whereas for most of the women included in the elagolix clinical trials, a screening BMD assessment as well as an assessment after 6 months of placebo treatment was available. For some patients who did not consent to enter one of the elagolix phase III extension studies with active treatment, follow-up measurements up to month 12 since baseline ($N = 63$) and month 18 ($N = 42$) were additionally included in the analysis.

Relationship between age and FN-BMD

Figure 1a describes the relationship between age and FN-BMD for the NHANES data set. BMD gradually increased with age starting from 8 years and up to ~ 20 years, followed by a steady decline in BMD over a period of 65 years. In premenopausal women who participated in elagolix phase III trials, FN-BMD at baseline was slightly higher for the same age range when compared with women from the NHANES data set.

Modeling of FN-BMD using RWD

The age-BMD relationship based on the NHANES data was appropriately described by a bi-exponential model. The estimated parameter values from the final FN-BMD model using NHANES data are listed in Table 2. The model-estimated FN_{max} was 1.08 g/cm^2 and the k_1 and k_2 rate constants were 0.153 1/year and 0.00747 1/year, respectively,

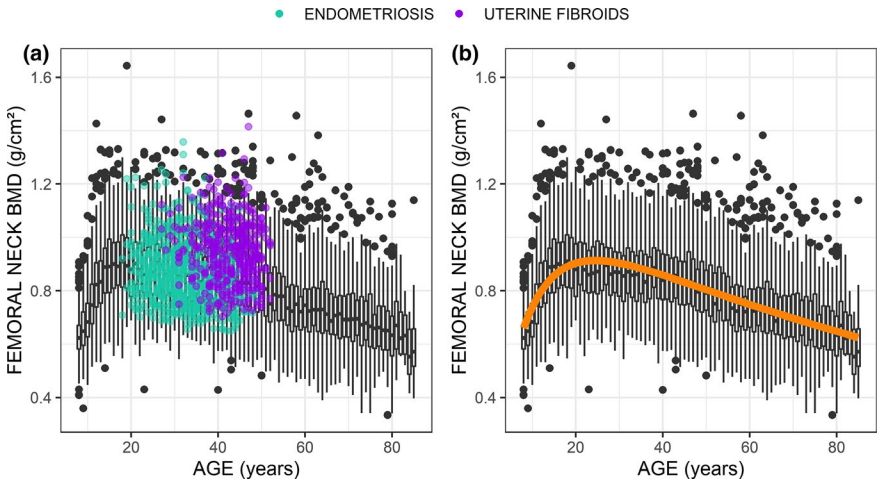

FIGURE 1 Observed and model-predicted femoral neck bone mineral density (FN-BMD) versus age using real-world data. Boxes and horizontal lines represent the interquartile range (IQR; 25th and 75th percentiles) and median of observed FN-BMD at each age category using National Health and Nutrition Examination Survey data. Lower and upper whiskers represent the smallest and largest value within 1.5-times IQR. Outlying data are represented as black dots. Boxplots are overlaid with FN-BMD data at baseline measured with Hologic machine type from elagolix clinical trials represented as colored dots (a) and with the median (solid line) of the model-predicted data (b)

TABLE 2 Parameter estimates for the real-world data FN-BMD model

Parameter	Estimate (SEE)	%RSE[a]	95% CI
FN_{max}, g/cm^2	1.08 (0.00477)	0.442	1.07–1.09
k_1, 1/year	0.153 (0.00273)	1.78	0.147–0.158
BMI on k_1[b]	0.868 (0.0358)	4.12	0.798–0.938
Black race on k_1[c]	0.149 (0.0187)	12.6	0.112–0.186
k_2, 1/year	0.00747 (0.000111)	1.49	0.00725–0.00769
BMI on k_2[b]	−1.08 (0.0285)	2.64	−1.13 to −1.02
Black race on k_2[c]	−0.271 (0.0118)	4.35	−0.295 to −0.248
Tobacco use on k_2[c]	0.0771 (0.0142)	18.4	0.0493–0.105

Abbreviations: BMI, body mass index; CI, confidence interval; FN-BMD, femoral neck bone mineral density; FN_{max}, maximum femoral neck bone mineral density; k_1, formation rate constant; k_2, resorption rate constant; RSE, relative standard error; SEE, standard error of estimate.

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

[b]Continuous covariates were centered to a reference value (median value of the population) and included in the model with a power function: $(\mathrm{cov}_{i,p}/ref_p)^{\theta_{i,p}}$.

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

reflecting the gradual increase between the ages of 8 and 20 years and the steady decline up to the age of 85 years. A covariate search on this model based on NHANES data alone suggested that BMI and Black race on k_1 and k_2 and smoking on k_2 are significant predictors of FN-BMD (Table 2; p value < 0.001).

The observed and model-predicted median FN-BMD using the base model parameter estimates over the studied age range is shown in Figure 1b. Overall, the RWD from NHANES is adequately described by the model over the entire age range. The model-predicted median FN-BMD of 0.896 and 0.842 g/cm^2 for the median observed age of patients with endometriosis and patients with UFs (32 and 43 years, respectively) is in the range of the observed FN-BMD 95% CI (0.727 g/cm^2, 1.30 g/cm^2) and (0.695 g/cm^2, 1.13 g/cm^2) from the phase III trials, respectively.

Modeling of FN-BMD using clinical trials data

The final FN-BMD model utilizing clinical trials data included a proportional error term and IIV on k_1 and k_2 (incorporating correlation using a block matrix). Factors to account for differences in baseline FN-BMD due to DXA scan machine types

were included in the model in addition to baseline *Z*-score on k_1 and k_2, Black race on k_2 and BMI on k_1.

The parameter estimates for the final FN-BMD model using clinical trials data informed by RWD as prior are listed in Table 3. The model-estimated FN_{max} was 1.53 g/cm^2, and the k_1 and k_2 rate constants were 0.0546 1/year and 0.0179 1/year, respectively. The differences in parameters between the RWD and clinical trial data model were quantified to ensure that the prior did not constrain the estimates to a biased value. Comparing the parameter estimates from the clinical trial data model to the model build without prior confirmed the appropriateness of the estimates. However, the usage of prior information stabilized the parameter estimation. The estimated relative standard error (%RSE) for the parameters in the FN-BMD model showed narrow CIs for all parameters (<35%). None of the 95% CIs for the parameters included the reference value, confirming the robustness of the parameters. IIV shrinkages on k_1 and k_2 rate constants were 39.4% and 41.9%, respectively.

Although significant shrinkage is present, the VPC for changes in BMD versus time demonstrated that the final model adequately described the central tendency, as well as the variability in the observed FN-BMD phase III data for patients with UFs and patients with endometriosis (Figure S3), with a slight overprediction of median bone loss for the endometriosis population. A comparison of the observed and model-predicted percentage change from baseline in FN-BMD at month 6 for patients with UFs is shown in Figure 2. The model-predicted median percentage change from baseline in FN-BMD of −0.3% at month 6 in patients with UFs, respectively, is in the range of the observed BMD changes at month 6 (95% CI: −0.7% to 0.2%).

Results on the effects of significant covariates in the final FN-BMD model (Figure S2) are described in Supplementary Results.

Longitudinal FN-BMD model simulations

Using the final BMD model and including the characteristics of the patient populations in elagolix phase III

TABLE 3 Parameter estimates for the clinical trial data FN-BMD model

Parameter	Estimate (SEE)	%RSE[a]	95% CI
Population value (θ)			
FN_{max}, g/cm^2	1.53 (0.0129)	0.844	1.51–1.56
k_1, 1/year	0.0546 (0.000610)	1.12	0.0534–0.0558
BMI on k_1[c]	0.0375 (0.0129)	34.4	0.0122–0.0628
Baseline *Z*-score on k_1[e]	0.187 (0.00444)	2.37	0.178–0.196
k_2, 1/year	0.0179 (0.000211)	1.18	0.0175–0.0183
Black race on k_2[d]	−0.284 (0.00397)	1.40	−0.292 to −0.276
Baseline *Z*-score on k_2[e]	−0.211 (0.00319)	1.51	−0.217 to −0.205
Factor for machine type Lunar[f]	0.164 (0.00149)	0.909	0.161–0.167
IIV (ω^2)			
IIV on k_1, %CV[b]	0.0260 (16.2)	8.88	0.0215–0.0305
IIV on k_2, %CV[b]	0.0110 (10.5)	9.36	0.00898–0.0130
Residual variability (σ^2)			
σ_1^2, Proportional	0.000598 (1.29×10^{-05})	2.16	0.000577–0.000619

Abbreviations: BMI, body mass index; CI, confidence interval; CV, coefficient of variation; FN-BMD, femoral neck bone mineral density; FN_{max}, maximum femoral neck bone mineral density; IIV, interindividual variability; k_1, formation rate constant; k_2, resorption rate constant; RSE, relative standard error; SEE, standard error of estimate.

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

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

[c]Continuous covariates, except the baseline *Z*-score, were centered 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:
$\left(1 + \theta_{k,BLZSCO} \times \left(BLZSCO_i - ref_{BLZSCO}\right)\right.$.

[f]Factor to account for differences in BMD measured with Hologic and Lunar machine types.

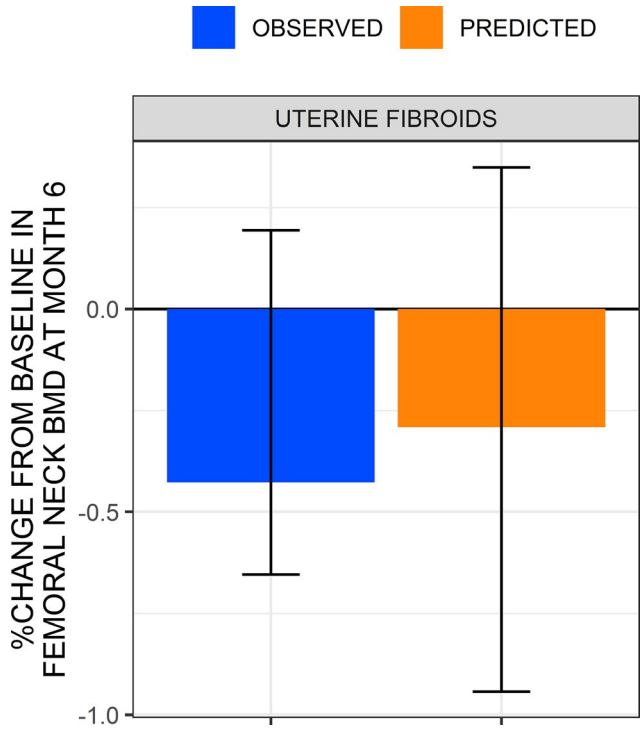

FIGURE 2 Observed and model-predicted percentage change from baseline in femoral neck bone mineral density (FN-BMD) at month 6 for the final model using clinical trials data of patients with uterine fibroids. Median (bar plots), 2.5th and 97.5th percentiles around the median (error bars) of the predicted percentage change from baseline in FN-BMD from elagolix clinical trials at month 6 are compared with the observed data

clinical trials, a trajectory of individual BMD changes over time beyond the clinical trial period (6 to 12 months) was simulated.

In Figure 3, the simulated FN-BMD and percentage change from baseline in FN-BMD over age are shown. Simulations suggest that premenopausal women with UFs (median age 43 years) may experience 4.8% (95% CI: 4.4% to 5.1%) natural loss in FN-BMD over 8 years, a period that resembles reaching menopausal age relative to the median age of this patient population. FN-BMD was predicted to decline by ~ 0.6% (95% CI: 0.3% to 0.9%) each year. Simulation results for the endometriosis population (Figure S4) are described in Supplementary Results.

Long-term prediction of postmenopausal risk of bone fractures in women with UFs

Patients with UFs are older by a decade and closer to menopause relative to patients with endometriosis (see Table 1). Elagolix is approved for the management of HMB associated with UF, therefore, long-term projections of longitudinal changes in BMD and its relation to future risk of fracture in this patient population informed drug development decisions. To extend the BMD model projections to clinically relevant predictions of future fracture risk, the FRAX tool was used.

The results of simulated FN-BMD, 10-year risk of hip fractures and MOFs, and proportion of patients in need of osteoporosis treatment from pre- to postmenopausal age are shown in Figure 4a,b, respectively. Based on model simulations, the median FN-BMD in the trial population would be 0.975 g/cm^2 at menopausal age (i.e., 51 years), which is associated with a 10-year risk of hip fracture of 0.08% and 10-year risk of MOFs of 2.3% based on the FRAX model. Based on the estimated trajectory of BMD loss over time, the median age where women would meet the risk-based thresholds to initiate osteoporosis treatment was predicted to be 72 years. At this age, the 10-year risk of hip fracture was 1.7% and MOF was 7.0%. Further, the proportion of subjects who would reach the risk-based threshold for initiation of osteoporosis treatment was 0% at age 51 and increased to 16.4% at age 72. For comparison, these predictions are consistent with the distribution of observed risk of hip fractures across age within the NHANES population and demonstrate external validation of the model predictions (Figure S5).

DISCUSSION

The association of decreased BMD and increased risk of osteoporotic fracture in postmenopausal women is well-established. Young premenopausal women have a low risk of nontraumatic fractures and the incidence and prevalence of fractures is orders of magnitude lower than in postmenopausal women.[3] However, the relationship between longitudinal changes in BMD in adult premenopausal women and the future risk of MOF after menopause has not been established. In addition, in randomized controlled clinical trials, BMD changes in premenopausal women are monitored over a relatively limited duration (i.e., 6–12 months) because routine BMD screening in healthy premenopausal women is not recommended, due to the lack of data relating incident fractures to BMD loss in this population of women. Hence, quantitative understanding of long-term effects on BMD in this population of women is limited to cross-sectional studies. Moreover, adverse changes in BMD caused by some medical treatments, such as chronic corticosteroids, chronic proton pump inhibitors, GnRH agonists or antagonists, injectable progestin-only contraceptives, etc., resulted in limited duration of use for the approved treatments, primarily due to lack of longitudinal BMD data in treated patients beyond the clinical trials' duration, and lack in understanding of the relationship between BMD loss in premenopausal women and future risk of bone fractures during postmenopausal age.[6,7,25,26] RWD provide valuable information to describe the natural history of physiological/

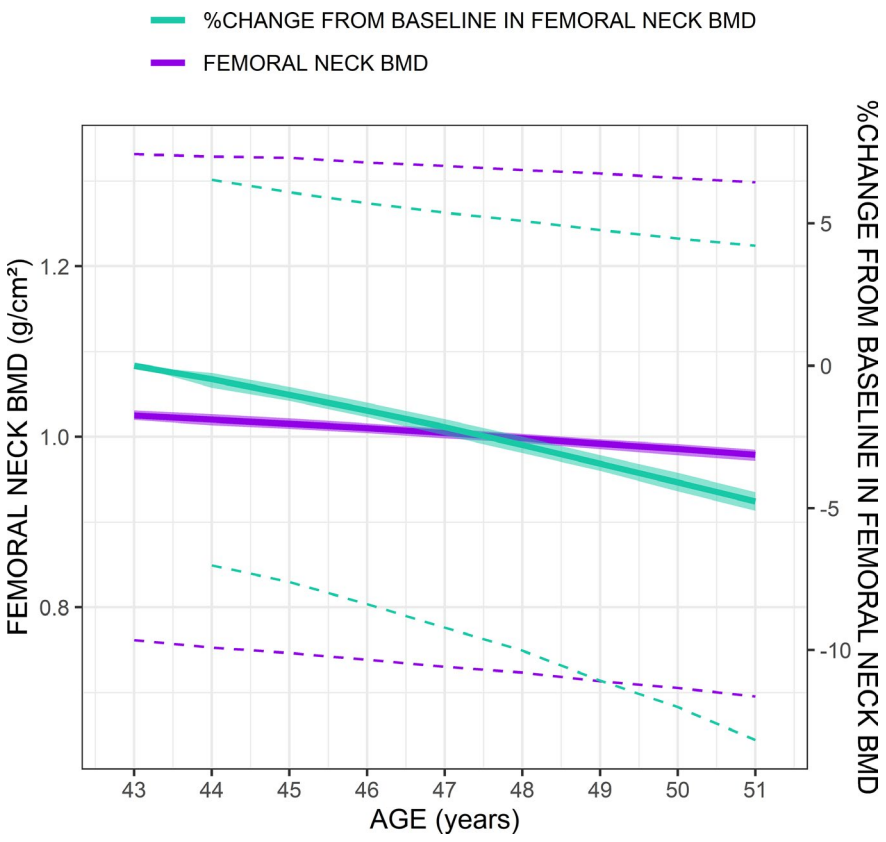

FIGURE 3 Simulated femoral neck bone mineral density (FN-BMD) and percentage change from baseline in FN-BMD over time up to menopausal age for patients with uterine fibroids. Lines and shaded regions represent median and 95% confidence interval of the median. Dotted lines represent the 95% prediction interval

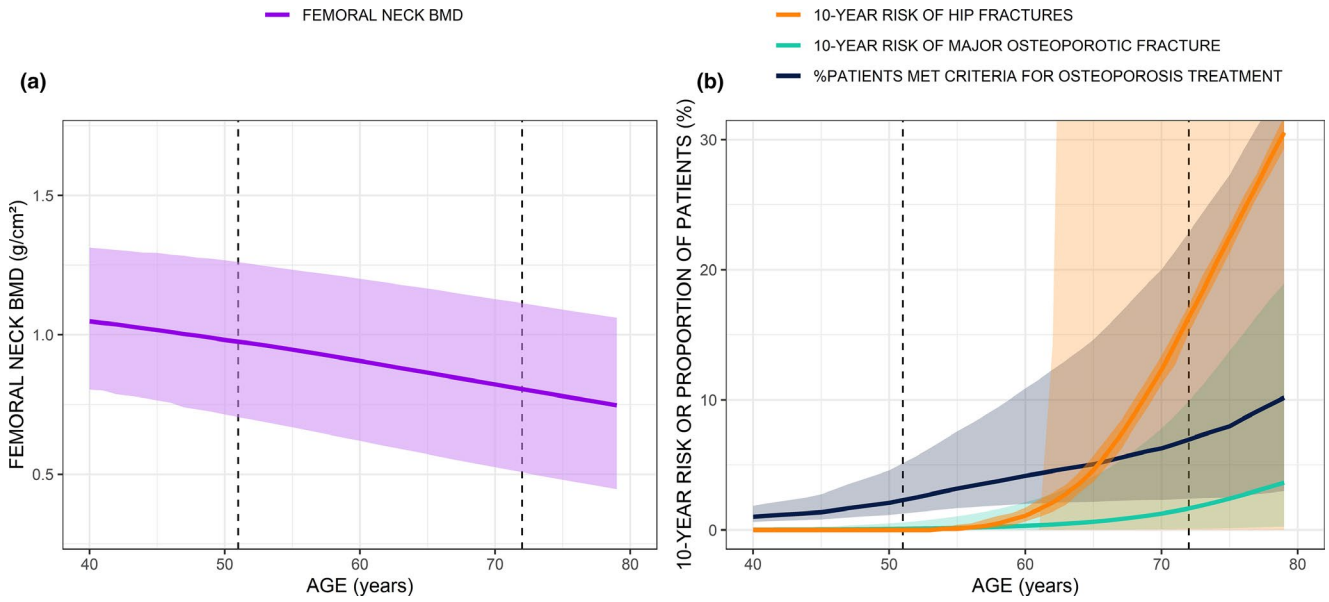

FIGURE 4 Predicted 10-year risk of hip and major osteoporotic fractures and proportion of patients with uterine fibroids (UFs) in need of osteoporosis treatment up to postmenopausal age. Lines and shaded regions represent predicted median and 95% prediction interval of the median for femoral neck bone mineral density (FN-BMD) (a), 10-year risk of hip fractures and major osteoporotic fractures and proportion of patients in need of osteoporosis treatment (b). The dashed vertical lines represent the median age when a typical patient with UFs may reach menopause (i.e., 51 years) and the estimated median age when patients with UFs were recommended to initiate osteoporosis treatment (i.e., 72 years)

pathophysiological events, and in the case of BMD changes, it offers an opportunity to contextualize the long-term safety profile in a given patient population to inform regulatory decision making beyond the observed clinical trial data, and especially when BMD loss is induced by medical therapies and is part of the benefit-risk evaluation.

To enhance understanding of the natural history of BMD in premenopausal women, publicly available RWD from

NHANES[11] were utilized to describe the dynamics of FN-BMD natural changes due to aging in untreated women of various demographics, using age as a surrogate for time. The integration of modeling and RWD to describe the clinical trials data enabled simulations of BMD changes over longer duration beyond the phase III trial's period. Although the elagolix phase III FN-BMD at baseline was slightly higher for the same age range of women in the NHANES data set, this small difference could be explained by the exclusion criteria of the elagolix phase III pivotal studies that excluded patients with endometriosis with DXA scan results of BMD corresponding to 1.5 or more SDs below normal (Z-score ≤ -1.5) at screening, or patients with UFs with a BMD T-score less than or equal to -1.5 at screening.[16,17] This indicates that the use of the NHANES BMD data as prior for analyzing elagolix placebo BMD data was appropriate. For clinical relevance, the BMD model simulation results at multiple timepoints (i.e., various ages) were used as input into the epidemiological FRAX model to translate the simulated BMD changes into a long-term postmenopausal fracture risk. The modeling approach was able to adequately describe the RWD data, as indicated by the VPCs, and the use of prior to model the elagolix trials data was also adequate as shown by the model diagnostics. The outcome of these analyses were longitudinal BMD simulations coupled with the FRAX predictions, which suggested that at menopausal age of 51 years, women with UFs have a projected 10-year risk of hip fracture of less than 1% and 10-year risk of MOF of 2.3%.

One of the limitations in this approach is related to the lack of long-term longitudinal data from each subject in the NHANES data set, which ideally would describe the BMD trajectories. It is worth highlighting that long-term longitudinal studies in premenopausal women are lacking, and the majority of studies are either short-term (i.e., 1 year) or cross-sectional only in small cohorts of patients.[3] In lieu of long-term longitudinal data on BMD in premenopausal women and given that age is a time factor, the large data set of 11,536 women in the NHANES RWD reflected the known physiology of gradual decrease in BMD after reaching peak bone mass (i.e., at 20–30 years) as women age and approach menopause,[27] therefore use of age as a surrogate for time in this modeling approach was appropriate to describe the longitudinal BMD relationship on a population level. Furthermore, the NHANES large data set with one measurement per subject was used as a prior and the elagolix phase III clinical trial data with two or more longitudinal BMD assessments per subject were then integrated using a combined utility of RWD and modeling to extend the value of the cross-sectional RWD.

Another limitation is the assumption that the clinical risk factors in the UF patient population (i.e., race, BMI, and current smoking status) from elagolix phase III trials used for the FRAX calculation of 10-year risk of fractures, is reflective of the entire patient population. This assumption is considered appropriate given that the phase III trials were enriched with patients with UFs that are expected to reflect the targeted patient population in the real world. Given the flexibility of the FRAX tool, it is plausible to conduct a theoretical sensitivity analysis with various additional clinical risk factors to evaluate the impact on the predicted risk (e.g., previous fractures, parental history of hip fractures, glucocorticoid use, rheumatoid arthritis, secondary osteoporosis, or heavy alcohol use), however, this was out of the scope in this work due to the need for actual patient demographics with such clinical risk factors in order to simulate BMD changes using the described modeling approach. Aging women may require the use of anabolic bone agents or other medications to slow down their bone loss. Use of such medications was not included as a factor in the long-term simulated BMD values, and once accounted for it may impact the longitudinal predictions by decreasing the future risk of fractures.

A previous analysis by Binkley et al.[28] investigated the impact of hypothetical drug-induced bone loss in premenopausal women in relation to the predicted fracture risk later in life. The authors used BMD distribution from the NHANES with varying degrees of hypothetical drug-induced loss in BMD to predict the probability of MOF using FRAX, and the resulting fracture risks were evaluated against treatment guidelines. In that study, the authors concluded that a hypothetical drug-induced BMD loss of 4–10% using cross-sectional BMD distribution at a certain age group of premenopausal women would be tolerated without reaching treatment thresholds. In our study, we extended the hypothetical scenario by Binkley et al. to a model-based approach using RWD across the age spectrum and clinical trials data in premenopausal patients with UFs and patients with endometriosis to predict longitudinal BMD changes using actual patients' demographics to predict the probability of fracture risk later in life. Our FRAX prediction results suggest that the estimated trajectory of BMD loss over time translate to a median age of 72 years where women would meet the risk-based thresholds to initiate osteoporosis treatment, consistent with clinical guidelines.[29]

To our knowledge, this is the first report that describes longitudinal changes in FN-BMD in premenopausal women across healthy, endometriosis, and UF patient populations, using a combined utility of RWD and modeling to quantitatively describe the BMD trajectory in premenopausal women, beyond the limited clinical trials data, and to translate this trajectory into long-term postmenopausal fracture risk. This model-based analysis will be useful for evaluating the effect of medical treatments that induce BMD loss in premenopausal women, and enables understanding of clinically relevant outcomes, such as the probability of MOF risk in this population, in order to inform appropriate duration of use for risk-benefit assessment of new medical treatments.

DATA SHARING 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 (e.g., 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. These 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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CONFLICT OF INTEREST

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

AUTHOR CONTRIBUTIONS

D.B., I.W., and M.S. wrote the manuscript. D.B., I.W., N.M.M., P.N., 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. 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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