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ARTICLE

Effect of Elagolix Exposure on Clinical Efficacy End Points in Phase III Trials in Women With Endometriosis-Associated Pain: An Application of Markov Model

Insa Winzenborg[1,†], Akshanth R. Polepally[2,*,†], Ahmed Nader[3], Nael M. Mostafa[3], Peter Noertersheuser[1] and Juki Ng[4]

Elagolix is an oral gonadotropin-releasing hormone antagonist approved by the US Food and Drug Administration (FDA) for the management of moderate-to-severe pain associated with endometriosis and in combination with estradiol/norethindrone acetate approved for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women. The objective of this work was to characterize the relationships between elagolix exposures and clinical efficacy response rates for dysmenorrhea (DYS) and nonmenstrual pelvic pain (NMPP) in premenopausal women enrolled in the pivotal phase III studies with moderate-to-severe pain associated with endometriosis. Relationships between elagolix average concentrations (C_{avg}) and efficacy responses (DYS and NMPP) were characterized using a nonlinear mixed-effects discrete-time first order Markov modeling approach. Only age was statistically significant for NMPP but not considered clinically relevant. This work indicates that the selection of elagolix dose is not determined based on tested patient demographics, baseline, or endometriosis disease severity measures in covariate analysis. In other words, the work suggests no preference of one regimen over the other to treat endometriosis-associated pain (DYS or NMPP) for any patient subpopulation based on tested covariate groups.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THIS TOPIC?

☑ Elagolix (150 mg q.d. and 200 mg b.i.d.) is an oral nonpeptide gonadotropin-releasing hormone antagonist that was approved for women with endometriosis-associated moderate-to-severe pain.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ How to best model correlated composite clinical end points to derive an exposure-efficacy relationship that supports dose justification?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ The elagolix exposure-efficacy relationships for the clinical end points were well-characterized by a model with two separate discrete-time Markov Chain models connected by a correlated eta term. Higher percentage of patients demonstrated DYS and NMPP response with increasing elagolix plasma concentrations. No baseline patient or disease covariates affected response to elagolix treatment; hence, selection of elagolix dose is not determined based on the tested patient demographics, baseline, or endometriosis disease severity measures in exposure-efficacy covariate analysis (i.e., no preference of one regimen over the other to treat endometriosis-associated pain (DYS or NMPP) for any patient subpopulation based on tested covariate groups).

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

☑ Exposure-efficacy analyses of co-primary pain end points for two distinct dosing regimens provided a useful framework to support dose justification for the treatment of moderate-to-severe pain associated with endometriosis.

Elagolix is an orally active, nonpeptide, competitive gonadotropin-releasing hormone (GnRH) antagonist approved by the US Food and Drug Administration (FDA) for the management of moderate-to-severe pain associated with endometriosis (Orilissa).[1,2] Also, it was recently approved for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women in combination with estradiol/norethindrone acetate

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†These authors contributed equally to this article.

[1]Clinical Pharmacology and Pharmacometrics, AbbVie Deutschland GmbH & Co. KG, Ludwigshafen am Rhein, Germany; [2]Clinical Pharmacology and Pharmacometrics, AbbVie Biotherapeutics Inc., Redwood City, California, USA; [3]Clinical Pharmacology and Pharmacometrics, AbbVie Inc., North Chicago, Illinois, USA; [4]Pharmaceutical Development, AbbVie Inc., North Chicago, Illinois, USA. *Correspondence: Akshanth R. Polepally (akshanth.r.polepally@abbvie.com)

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(Oriahnn).[3] Elagolix is rapidly absorbed from the gastrointestinal tract with time to mean maximum observed plasma concentration (T_{max}) values of ~ 1 hour and an apparent terminal phase elimination half-life of 4–6 hours. Exposure of elagolix is approximately dose proportional from 100–400 mg twice daily.[4,5]

Elagolix suppresses pituitary secretion of luteinizing hormone and follicle-stimulating hormone, ovarian production of estradiol and progesterone, and ovulation in a dose-dependent manner.[5,6] In contrast to GnRH agonists, which have a delayed onset of action following initial stimulation of gonadotropic and gonadal hormones,[7,8] GnRH antagonists have a rapid onset of action and do not produce an initial hormonal flare effect. Elagolix has advantages over peptide GnRH antagonists as it is orally bioavailable[4,9] and can be readily discontinued if necessary.

Two double-blind, randomized, 6-month, phase III trials were conducted to evaluate the effects of 2 doses of elagolix—150 mg once daily and 200 mg twice daily as compared with placebo in women with surgically diagnosed endometriosis and moderate or severe endometriosis-associated pain.[1] Both doses of elagolix were effective in improving dysmenorrhea (DYS) and nonmenstrual pelvic pain (NMPP) during a 6-month period in women with endometriosis-associated pain and were associated with hypoestrogenic adverse effects.[1]

Exposure-efficacy analyses were conducted to further evaluate the relationships between elagolix concentrations and the two co-primary end points (DYS and NMPP). The traditional approach to modeling of relationships between exposure and dichotomized responses ("response" or "no response") that are assumed to be independent of each other involves logistic regression analysis. However, successive measurements collected frequently over time for each individual are not independent.[10] Markovian models allow, however, a more accurate characterization of the transitions between responder and nonresponder states over time.[11] In this regard, Markov models have proved useful in characterizing transitions in responder states.[10,12] However, modeling all combinations of responses to two end points plus dropouts would lead to estimation of a large number of transition rates that make the interpretation of parameters challenging and result in a less stable model.

We developed two separate discrete-time Markov models for DYS and NMPP to characterize relationships between elagolix exposures and response rates and introduced correlation between both model parts by correlated interindividual variability (IIV) on transition probabilities (**Figure 1**). The model was developed for the women enrolled in the 2 pivotal, 6-month, phase III studies plus their respective open-label 6-month extension studies. We then used this model to evaluate the impact of patient-specific characteristics on the DYS and NMPP response rates.

METHODS

Data

Study design. Data from two replicate, double-blind, placebo-controlled, 6-month, pivotal phase III studies in women with endometriosis with associated moderate-to-severe pain (Elaris endometriosis (EM)-I (NCT01620528) and Elaris EM-II (NCT01931670)) and the respective 6-month extension studies (Elaris EM-I-ext (NCT01760954) and Elaris EM-II-ext (NCT02143713))[1] (**Figure S1**) were used in model development. Patients (n = 1,689) received elagolix 150 mg q.d., elagolix 200 mg b.i.d., or placebo orally for 6 months. Patients who continued into the extension studies (n = 1,002) received an additional 6 months of treatment with elagolix or began 6 months of treatment with elagolix if they previously received placebo. Patients on active treatment in the pivotal studies continued the same treatment in the extension studies and patients on placebo in the pivotal study were randomized 1:1 to elagolix 150 mg q.d. or 200 mg b.i.d. for the extension studies. The studies used compliance packaging to dispense the study drug to study patients, which provided exact dosing times for the majority of doses for the pharmacokinetic analysis.[13] The studies were conducted in accordance with Good Clinical Practice guidelines and ethical principles that have their origin in the Declaration of Helsinki. The protocols and informed consent forms were approved by the institutional review boards and written informed consents were provided

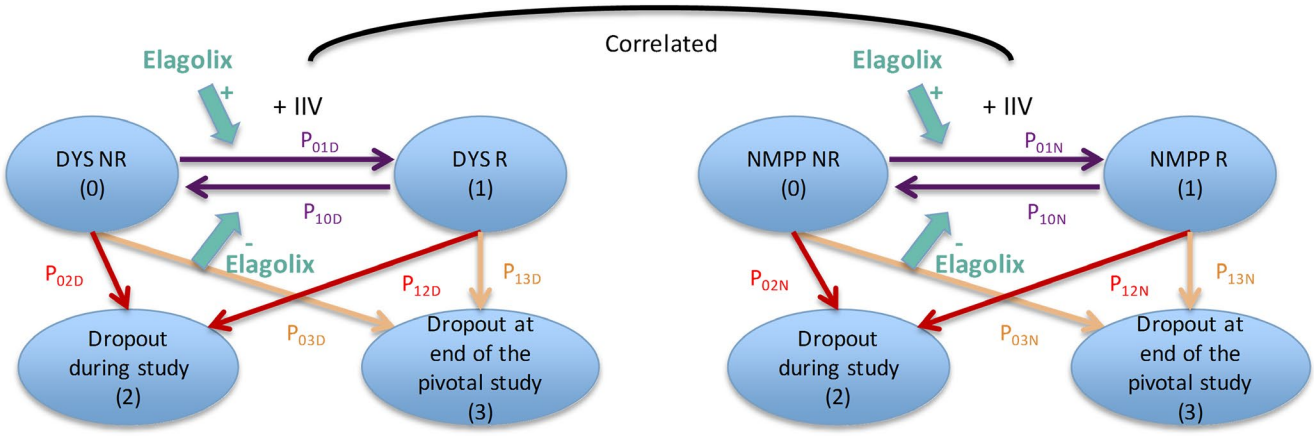

Figure 1 Schematic of the Markov Chain model. DYS, dysmenorrhea; IIV, interindividual variability; NMPP, non-menstrual pelvic pain; NR, nonresponder state; P_{ij}, i to j transition probability where i can take 0 or 1 and j can take 0, 1, 2, or 3 (P_{01}, P_{10}, P_{02}, P_{12}, P_{03}, and P_{13}) for DYS and NMPP as designated by letters "D" and "N"; R, responder state.

by all patients before any study-related procedures were performed.

Clinical end points. The responses for the primary efficacy end points of DYS and NMPP were collected daily in an e-diary using mutually exclusive scales as measured by the Daily Assessment of Endometriosis Pain.[1,14,15] Each of these end points was measured as a clinically meaningful reduction in the pain score (on a scale ranging from 0 (no pain) to 3 (severe pain)) and a decreased or stable use of rescue analgesic agents, as recorded in a daily electronic diary (see **Supplementary Information** for complete details of determination of responder status).

Exposure variable. Patient-specific elagolix exposures (monthly averages of daily average concentrations (C_{avg}) and monthly averages of daily trough plasma concentration (C_{trough}) values) were derived based on empirical Bayes estimates from a previously developed population pharmacokinetic model[13] and used in the exposure-efficacy model of the clinical end points. These exposures were generated after accounting for individual patient compliance rates. There were no systematic differences in compliance observed between the treatment arms (data on file).

Covariate data. Following covariates were investigated for influence on clinical end points (DYS or NMPP):

- Demographics: age, weight, body mass index, race (white vs. black), ethnicity (Hispanic yes/no), geographic region (United States vs. outside of the United States);
- Baseline pain scores: DYS or NMPP (tested in their respective model component);
- Baseline hormone level: estradiol, follicle-stimulating hormone, luteinizing hormone, progesterone;
- Time since endometriosis diagnosis: < 2 years vs. 2 to < 5 years vs. ≥ 5 years;
- Disease characteristics (during screening period): number of bleeding days, intensity of menstrual periods (none-to-light vs. moderate vs. heavy);
- Previous GnRH therapy;
- Baseline analgesic use: none vs. nonsteroidal anti-inflammatory drugs vs. narcotics vs. narcotics + nonsteroidal anti-inflammatory drugs;
- Tobacco use or alcohol use (yes or no).

The baseline for covariates was defined as the last nonmissing value collected before the first dose of study drug. The baseline pain score was defined as the average of the daily values reported during the last 35 calendar days in the screening period prior to day 1.

Data exclusions. Patients who received placebo treatment in a pivotal study and were subsequently enrolled in a respective extension study were excluded as their responder status was confounded by the baseline pain score at month 6 from the pivotal study (i.e., the placebo effect was included in the responder status). Patients with missing responder information and patients who were randomized but not dosed were excluded from the analysis.

Missing continuous covariates were assigned with estimated median values across the analysis population. Missing primary end point responses (DYS and NMPP) for months in between known values were imputed using the last observation carried forward values. In cases of premature discontinuations, a dropout flag was set for the dropout month and handled in the dropout model.

Software and data analysis. The exposure-efficacy model for the clinical end points was built using nonlinear mixed-effects modeling (NONMEM, version 7.3.0; ICON Development Solutions, Hanover, MD) compiled with the GNU Fortran compiler (version 4.8.3) by using the Laplacian method with conditional estimation. The Stepwise Covariate Model building tool of Perl-speaks-NONMEM (version 4.6.0) was implemented for forward selection and backward elimination of covariates. Model evaluation was performed using goodness-of-fit (GOF) plots, visual predictive checks (VPCs), and bootstrap analyses.

Model development

Model structure. Information regarding model structure is provided in the Results section.

Model building and selection. Modeling was initiated by developing a placebo effect model using placebo data. IIV was tested on transition probabilities between the two response states (P_{01} and P_{10}). Various functions of increasing complexity, such as drug effect (stimulatory or inhibitory maximum effect (E_{max}) models), dosing regimen effect (q.d. vs. b.i.d. dosing), covariates, and dropouts were tested for influence on the model. The effect of drug on transition rates between response states was modeled as a function of exposure, using monthly averages of daily C_{avg} and C_{trough} as elagolix exposure metrics. The exposure-efficacy end point relationships for each of the transition rates were explored using E_{max} equations. The selection of the exposure-efficacy model was based on the likelihood ratio test, precise parameter estimates, physiologically plausible parameter estimates, and VPCs. Equations describing the final model are presented in the Results section.

Covariate selection. Relevant covariates on transition probabilities were investigated in placebo and elagolix effect model components. All statistical tests in forward selection were assessed at the 0.01 significance level and backward elimination were assessed at the 0.001 significance level. The covariates were tested on Pla_{01}, Pla_{10}, half-maximal effective concentration $(EC_{50})_{,01}$, $EC_{50,10}$, $E_{max,01}$, and $E_{max,10}$ as described in **Supplementary Information**.

Final model evaluation

The final model was investigated for its adequacy using GOF plots, VPCs, simulation-based responses vs. observed responses, and model-predicted dropouts vs. observed dropouts. A bootstrap analysis (random sampling of subjects from the original dataset with replacement) was

conducted in order to check the robustness of the model and the precision of the parameter estimates.

RESULTS

Patients and data

The elagolix exposure variable of monthly means of daily average plasma concentrations and trough concentrations (C_{avg} and C_{trough}) was obtained from a population pharmacokinetic analysis.[11] The overall mean (5–95% percentiles) predicted daily C_{avg} and C_{trough} values were 46.5 (14.2–99.9) ng/mL and 1.34 (0.0634–5.58) ng/mL, respectively, for the 150 mg q.d. regimen and were 130 (38.2–262) ng/mL and 9.30 (0.204–34.8) ng/mL, respectively, for the 200 mg b.i.d. regimen.

The response variables of DYS and NMPP were assessed as described in the Methods section and in the **Supplementary Information**, and patients were classified at each month (28 days) as responders or nonresponders for each variable, or as having dropped out. A total of 1,671 women randomized in the pivotal phase III studies[1] were included in the exposure-efficacy analyses, providing 12,143 observations per DYS and NMPP end points. Across the 2 studies, 475 patients received elagolix 150 mg q.d., 477 patients received elagolix 200 mg b.i.d. and 734 patients received placebo for the 6-month treatment period in the pivotal studies, followed by optional enrollment and treatment with elagolix (150 mg q.d. or 200 mg b.i.d.) in the extension studies (**Figure S1**). Fourteen patients with missing responder information and two that were randomized and not dosed were excluded from the analyses. A summary of the demographic characteristics for the patients included in the analysis is presented in **Table 1**.

Table 1 Demographic and baseline characteristics of the patients included in the exposure-response analysis

Characteristic	All patients (*N* = 1,671)
Treatment, *n* (%)	
Placebo	731 (44)
Elagolix 150 mg q.d.	469 (28)
Elagolix 200 mg b.i.d.	471 (28)
Race, *n* (%)	
White and other	1527 (91)
Black	144 (9)
Age, years	32 (18–49)
Weight, kg	74 (40–148)
Body mass index, kg/m^2	28 (16–55)
Baseline pain scores	
Baseline DYS score	2.2 (0.0–3.0)
Baseline NMPP score	1.6 (0.1–3.0)
Baseline estradiol, pg/mL	83.3 (3.2–839.0)
Baseline FSH, IU/L	8.4 (0.9–126.6)
Baseline LH, IU/L	8.0 (0.2–118.8)
Baseline progesterone, ng/mL	0.7 (0.1–26.4)
Time since endometriosis diagnosis, *n* (%)	
< 2 years	588 (35)
2 to < 5 years	597 (36)
5 to < 10 years	450 (27)
≥ 10 years	36 (2)
Previous GnRH therapy, *n* (%)	
No	1234 (74)
Yes	437 (26)
Number of bleeding days during screening period	5.3 (0.0–17.0)
Intensity of menstrual periods in screening period, *n* (%)	
None	806 (48)
Spotting	3 (<1)
Light	44 (3)
Moderate	368 (22)
Heavy	450 (27)

Data are presented as mean (range) unless otherwise indicated.
DYS, dysmenorrhea; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; NMPP, non-menstrual pelvic pain.

Structural model

A discrete-time Markov Chain model (**Figure 1**) was built describing monthly transitions between responder states based on monthly means of elagolix daily C_{avg}. The transition states of the Markov Chain were defined for each patient for each efficacy end point (DYS and NMPP) as no response (DYS NR or NMPP NR, indicator = 0), response (DYS R or NMPP R, indicator = 1), dropout at any time during the study (indicator = 2), and dropout after month 6 (indicator = 3), as shown in **Figure 1** and described in the Methods section. Dropout after month 6 (i.e., at the end of the pivotal studies) was estimated separately because participation in the extension studies was voluntary. Several patients (687) did not participate in the extension studies; thus, dropout rates after month 6 were higher than dropout rates during the pivotal studies. All subjects are assumed to start in nonresponder state at month 0.

The DYS and NMPP end points were simultaneously modeled by introducing correlation between the IIV parameters of the respective nonresponder to responder transitions (P_{01D} and P_{01N}). The structural model described the transition between the responder and nonresponder states and dropouts from these response states (**Figure 1**). The model included a first-order Markovian feature, implying that the probabilities of patients being in the responder or nonresponder states at each month were conditioned on their state at the previous month.

The course of the monthly DYS and NMPP responder states were modeled via transitions between model states, which were characterized by respective transition probabilities $P_{ij,}$ where can take 0 or 1 and j can take 0, 1, 2, or 3 (P_{01}, P_{10}, P_{02}, P_{12}, P_{03}, and P_{13}), estimated in logit transformation (e.g., Eq. 1).

$$P_{01} = \frac{\exp\left(\text{logit}\left(P_{01}\right)\right)}{1+\exp\left(\text{logit}\left(P_{01}\right)\right)} \quad (1)$$

The transition probabilities are later denoted as D for DYS and N for NMPP (e.g., P_{01D}).

Placebo and drug effect models

The transitions between responder state and nonresponder state were characterized in a sequential manner: first, a

placebo model was built followed by drug effect model as described below.

Placebo model. A placebo model was built using data from the placebo arms in the pivotal studies. Placebo data were modeled using expressions for the logit transformed parameters as shown in Eq. 2:

$$\text{logit}\left(P_{01}\right) = \text{Pla}_{01} + \text{eta}_1 \quad (2)$$

where P_{01} represents the probability of achieving a responder state from the nonresponder state, Pla_{01} is the probability of achieving a responder state from the nonresponder state when treated with placebo, and eta_1 is the IIV parameter on P_{01}.

The IIV was tested on transition probabilities between the two states (P_{01} and P_{10}). However, the IIV was dropped from the P_{10D} and P_{10N} parameters due to model instability. As mentioned above, the correlation between the IIV parameters for P_{01D} and P_{01N} was estimated. No random effect on the dropout transition probabilities was estimated because the patients could only drop out once during the trial, resulting in a maximum of one observation per patient.

Elagolix effect. The elagolix effect was modeled using the DYS and NMPP responder data generated from the elagolix treatment arms from the pivotal studies and their extensions. In this process, monthly elagolix exposures (C_{avg}) were tested to describe the elagolix effect on transitions from nonresponder to responder and vice versa by maximal probability (E_{max}) models (stimulatory and inhibitory models) on the logit transformed parameters.

For example:

$$\text{logit}\left(P_{01}\right) = \text{Pla}_{01} + \text{Emax}_{01} * \frac{C_{avg}}{\text{EC50}_{01} + C_{avg}} + \text{eta}_1 \quad (3)$$

where, $E_{max,01}$ is the maximum probability (in logit scale) of achieving the transition from nonresponder state to the responder state, $EC_{50,01}$ is the elagolix monthly C_{avg} for half-maximal probability (in logit scale) of achieving the transition from nonresponder state to the responder state, and C_{avg} is the monthly average of daily average elagolix concentrations. No elagolix effect was implemented on the transitions representing dropouts from the nonresponder or responder states (P_{02}, P_{12}, P_{03}, and P_{13}).

Elagolix monthly C_{avg} on DYS transitions (P_{01D} and P_{10D}) was tested using an E_{max} model (Eq. 3). Two EC_{50} parameters ($EC_{50,01D}$ and $EC_{50,10D}$) were estimated for the P_{01D} and P_{10D} transitions. A parsimonious model with the same EC_{50} parameter on both the transitions was significantly worse (change in objective function value, Δ(OFV) = +10). Similar to DYS, the elagolix monthly C_{avg} was introduced on NMPP transitions (P_{01N} and P_{10N}). Having the same EC_{50} on both the transitions ($EC_{50,01N} = EC_{50,10N}$) resulted in better precision for parameter estimates (with similar OFV) compared with the model with different EC_{50} parameters for the transitions. In the next step, introducing IIV on EC_{50} or E_{max} values led to unstable model results and shrinkage values of ~ 60% and, hence, IIV on these parameters was not included in further analyses.

A model with monthly averages of elagolix daily C_{trough} as an exposure metric in the drug effect model was also explored. However, the model with monthly C_{avg} was found to be a better model than the one with monthly averages of daily C_{trough} (ΔOFV = +37). Therefore, the model with monthly C_{avg} was used for further development.

Regimen effect (q.d. vs. b.i.d. dosing). During model development, VPCs were carried out to evaluate model performance. The VPCs indicated model misspecifications with underprediction of DYS response rates for the elagolix 200 mg b.i.d. regimen and overprediction of DYS response rates for the elagolix 150 mg q.d. regimen. The NMPP response rates were adequately predicted for both elagolix dosing regimens. In order to improve the model in terms of prediction of DYS response rates, regimen effect (200 mg b.i.d. vs. 150 mg q.d.) was introduced on E_{max} parameters associated with the DYS transitions ($E_{max,01D}$ and $E_{max,10D}$). The regimen effect on E_{max} parameters significantly improved the model (ΔOFV = –19) and resulted in better predictions of DYS response rates for both dosing regimens. The regimen effect was also evaluated on E_{max} parameters ($E_{max,01N}$ and $E_{max,10N}$) of NMPP, but it did not significantly improve the model (ΔOFV < 6.63). The model with monthly C_{avg} as elagolix effect, with regimen effect on E_{max} parameters associated with the DYS transitions, was designated as the base model.

Modeling dropouts. Dropout was modeled in two states: dropouts during the study and dropouts at the end of month 6 (end of the pivotal studies). During this step, dropout rates that were similar and could be combined to simplify the model and improve model stability were also explored. As a result, the probabilities of dropping out from either the responder or nonresponder states were estimated with a common parameter for DYS ($P_{02D} = P_{12D}$) and with separate parameters for NMPP (P_{02N} and P_{12N}), and the dropout probabilities after 6 months associated with DYS or NMPP from either the responder or nonresponder states were estimated by a single parameter (i.e., $P_{03D} = P_{13D} = P_{03N} = P_{13N}$).

Covariate analysis

Covariates for demographic characteristics, baseline hormone levels, disease severity measures, baseline analgesic use, and prior GnRH therapies were evaluated as described in the Methods section. Covariates were tested on placebo transition rates (Pla_{01D}, Pla_{10D}, Pla_{01N}, and Pla_{10N}), EC_{50} parameters ($EC_{50,01D}$, $EC_{50,10D}$, $EC_{50,01N}$, or $EC_{50,10N}$), and E_{max} parameters ($E_{max,01D}$, $E_{max,10D}$, $E_{max,01N}$, and $E_{max,10N}$) that describe the drug effect on transition rates (P_{01D}, P_{10D}, P_{01N}, and P_{10N}).

Following forward selection and backward elimination procedures in the placebo model, baseline DYS and NMPP scores were significant on the respective placebo transition probabilities (Pla_{01D}, Pla_{10D}, Pla_{01N}, and Pla_{10N}). In the elagolix effect model, only age was a significant covariate on the EC_{50} parameter associated with NMPP ($EC_{50,01N} = EC_{50,10N}$);

no covariate was statistically significant for DYS. The final model parameter estimates are presented in **Table 2**.

Summary of discrete-time Markov Chain exposure-efficacy model results

For placebo, the DYS response probability of transitioning from responder to nonresponder (Pla_{10D} = 0.40) was higher than that from nonresponder to responder (Pla_{01D} = 0.10) whereas the NMPP response probabilities of transitioning from responder to nonresponder and vice versa were similar (Pla_{10N} = 0.19 and Pla_{01N} = 0.17). As expected, the dropout probabilities after 6 months were estimated to be higher than those for the preceding monthly dropout probabilities due to the fact that participation in the extension studies was voluntary and some patients did not consent to participate.

In the elagolix effect model, the only significant covariate was age on the EC_{50} parameter ($EC_{50,01N}$ = $EC_{50,10N}$) associated with the NMPP portion of the model. The effect of age on the EC_{50} parameter associated with NMPP is illustrated by the %NMPP responders at month 3 vs. age quartiles in **Figure 2**. Comparing patients who were 22 years old with those who were 32 years old (i.e., median age), the %NMPP responder rate for a 22-year-old was predicted to be ~ 7 percentage points lower. Comparing patients who were 42 years old with those who were 32 years old, the %NMPP responder rate for a 42-year-old was predicted to be 3–5.5 percentage points higher. There was no statistically significant covariate for DYS.

The NONMEM model code of the final model is provided in the **Supplementary Material**.

Final model evaluation

The GOF for the final model was evaluated graphically and is presented in **Figure S2**. The GOF plots indicated that the

Table 2 Parameter estimates and bootstrap summaries for the final population exposure-response models for DYS and NMPP

	Final model	Bootstrap evaluation
Parameter	**Population estimate**	**2.5th and 97.5th percentiles**
DYS		
Transition 01 (nonresponder to responder)		
Pla_{01D}	0.0995[a]	0.0863, 0.114
$E_{max,01D}$	2.42	1.85, 3.28
$EC_{50,01D}$	36.1[b]	15.1, 69.2
BLDYS on logit Pla_{01D}	−0.282	−0.373, −0.194
Transition 10 (responder to nonresponder)		
Pla_{10D}	0.402[a]	0.361, 0.448
$E_{max,10D}$	−3.03	−5.00, −2.00
$EC_{50,10D}$	134[b]	61.7, 288
BLDYS on logit Pla_{10D}	0.826	0.305, 2.03
REGEFF on $E_{max,01D}$ and $E_{max,10D}$	1.30	1.10, 1.53
IIV on P_{01D}	1.26	1.04, 1.54
NMPP		
Transition 01 (nonresponder to responder)		
Pla_{01N}	0.168[a]	0.146, 0.190
$E_{max,01N}$	1.23	0.801, 1.90
$EC_{50,01N}$ = $EC_{50,10N}$	53.8[b]	8.13, 135
Age on $EC_{50,01N}$ = $EC_{50,10N}$	−0.0234	−0.171, −0.0088
BLNMPP on logit Pla_{01N}	−0.422	−0.567, −0.302
Transition 10 (responder to nonresponder)		
Pla_{10N}	0.195[a]	0.169, 0.223
$E_{max,10N}$	−1.43	−2.20, −0.969
IIV on P_{01N}	2.17	1.83, 2.65
Covariance between IIV on P_{01D} and IIV on P_{01N}	1.64	1.40, 1.88
Dropout transitions		
P_{02D}/P_{12D}	0.0459[a]	0.0423, 0.0497
P_{02N}	0.0522[a]	0.0479, 0.0573
P_{12N}	0.0375[a]	0.0323, 0.0435
P_{03D} = P_{13D} = P_{03N} = P_{13N}	0.242[a]	0.211, 0.275

P_{ij}, *i* to *j* transition probability where i can take 0 or 1 and *j* can take 0, 1, 2, or 3 (P_{01}, P_{10}, P_{02}, P_{12}, P_{03}, and P_{13}) for DYS and NMPP as designated by letters "D" and "N"Pla_{ij}, *i* to *j* transition probability with placebo where *i* and *j* can take 0 or 1 (Pla01, Pla10) for DYS and NMPP as designated by letters "D" and "N." BLDYS, baseline dysmenorrhea score; BLNMPP, baseline nonmenstrual pelvic pain score; DYS, dysmenorrhea; $EC_{50,ij}$, elagolix monthly average concentration for half-maximal probability (in logit scale) of achieving the transition from *i* to *j*; $E_{max,ij}$, maximum probability to (in logit scale) of achieving the transition from *i* to *j*; IIV, interindividual variability; NMPP, non-menstrual pelvic pain; REGEFF, drug regimen effect (200 mg b.i.d. vs. 150 mg q.d.).
[a]Estimated in logit transformation; transformed back for table.
[b]Estimated in exponential transformation (base 10); transformed back for table.

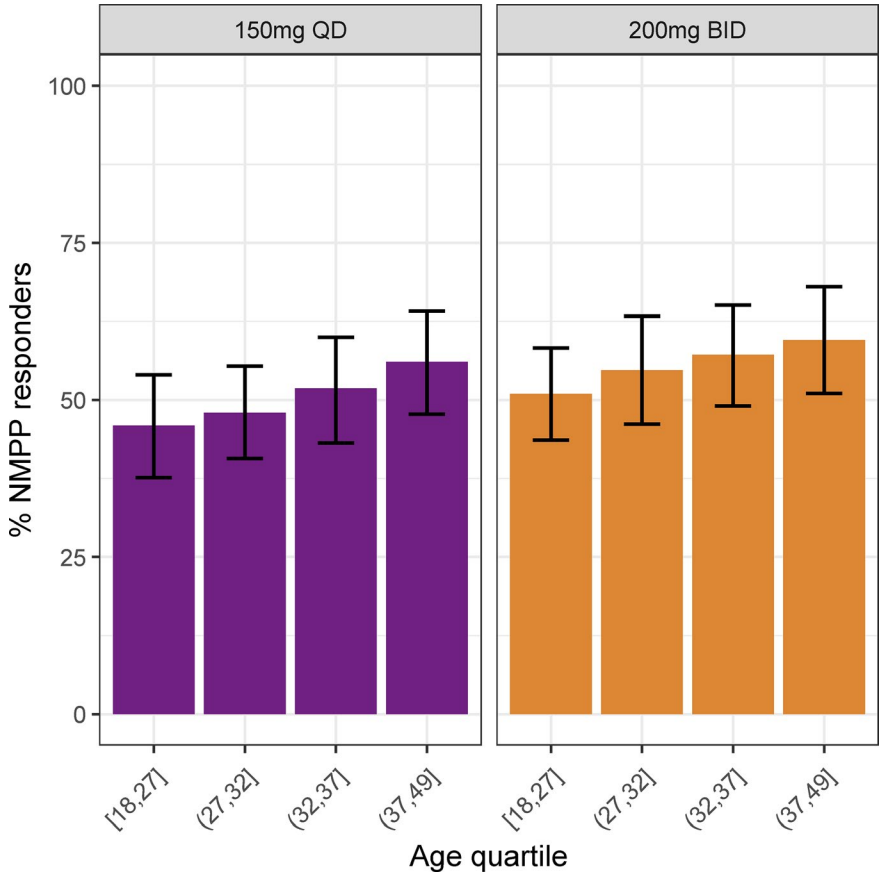

Figure 2 Effect of age (in years) on NMPP response rate at month 3. NMPP, nonmenstrual pelvic pain.

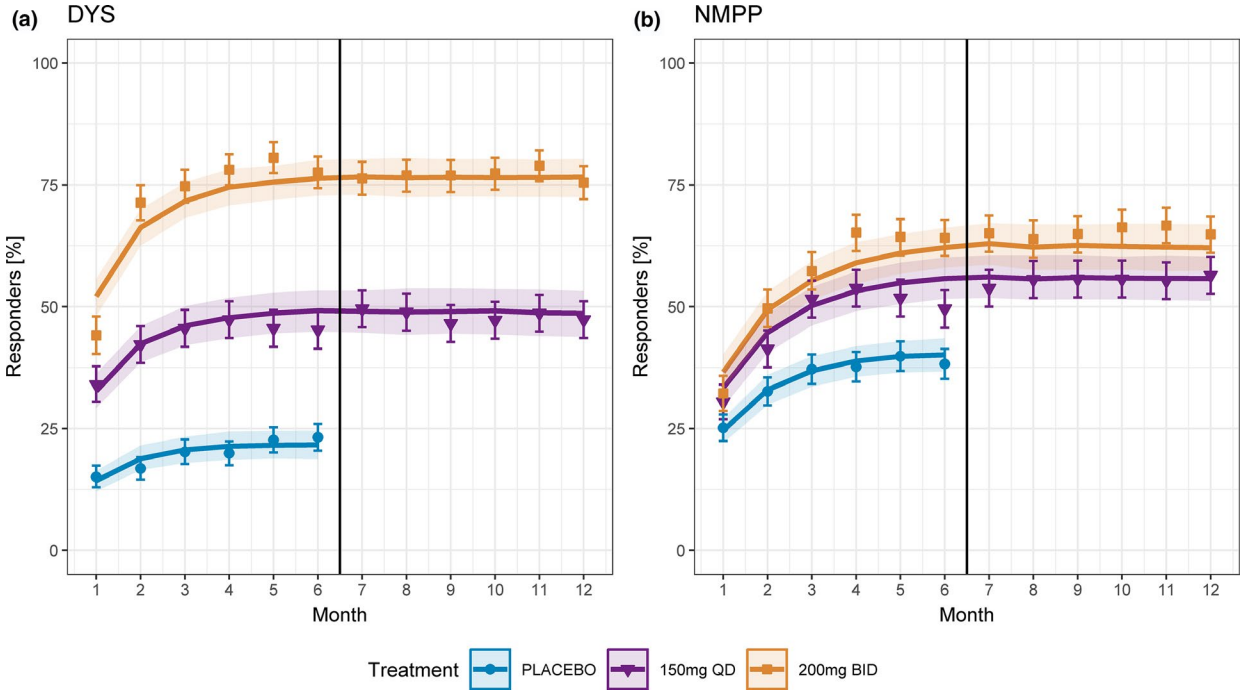

Figure 3 Exposure-efficacy analyses visual predictive checks for DYS and NMPP. DYS, dysmenorrhea; NMPP, non-menstrual pelvic pain. Visual predictive checks were created with 250 replicates each. Symbols with 90% confidence intervals represent observed data. Solid lines and shaded regions represent the median of the simulated data and 90% confidence intervals.

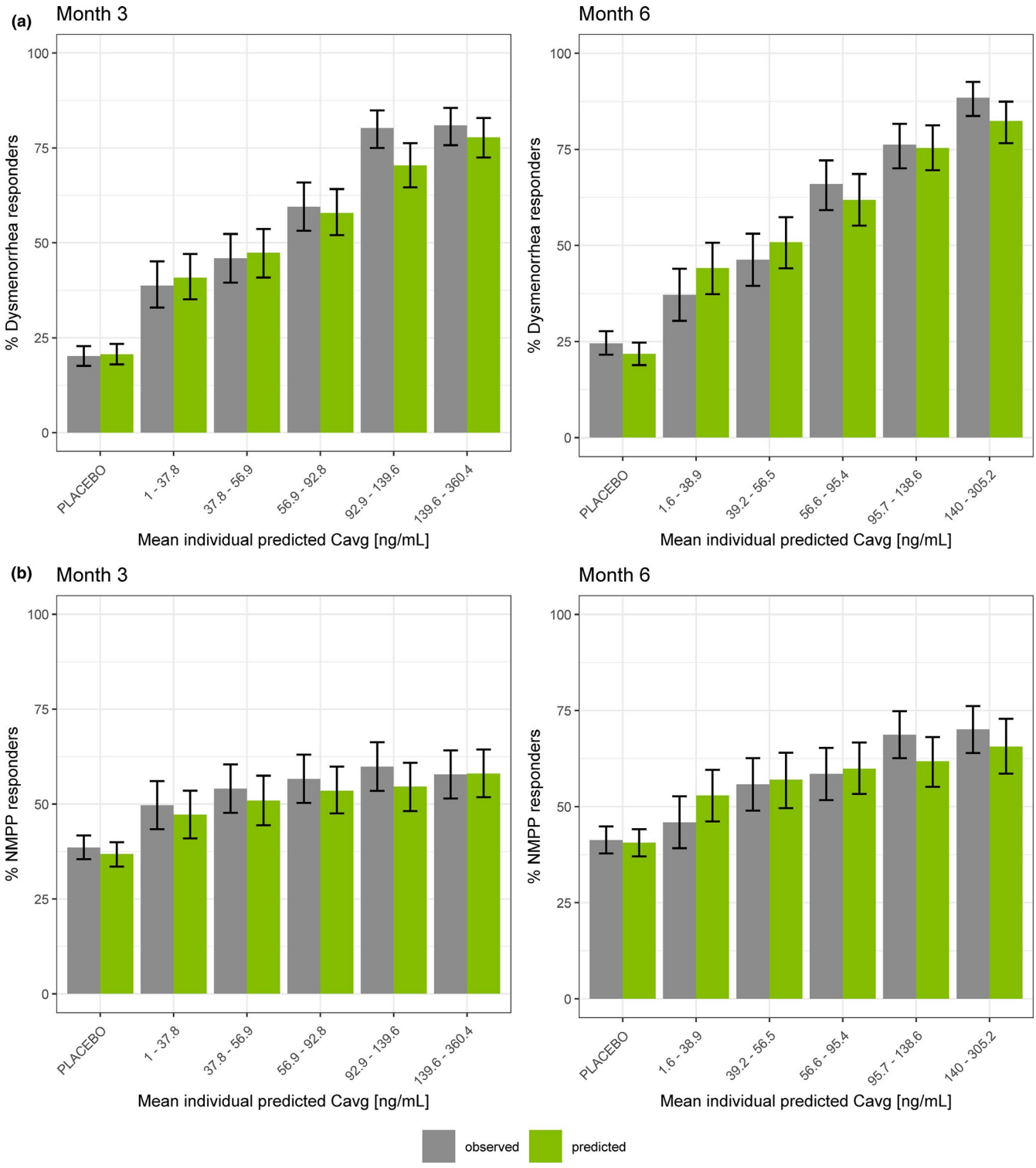

Figure 4 Observed vs. model-predicted response rates at month 3 and month 6 for elagolix concentration quintiles and placebo. Response rates of DYS at monthe 3 and 6 (top panel) and NMPP at month 3 and 6 (bottom panel). C_{avg}, monthly averages of daily average plasma concentration; DYS, dysmenorrhea; NMPP, non-menstrual pelvic pain.

monthly predicted transition probabilities (P_{01} and P_{10} and P_{02}/P_{03} and P_{12}/P_{13}) for DYS and NMPP were in agreement with the respective observed percentages and, thus, confirm that the discrete-time, first-order Markov Chain model for DYS and NMPP adequately described the observed percentages over time. The VPCs for the analysis (**Figure 3**) and the results of simulations for DYS and NMPP at month 3 and month 6 in comparison with observed data (**Figure 4**;

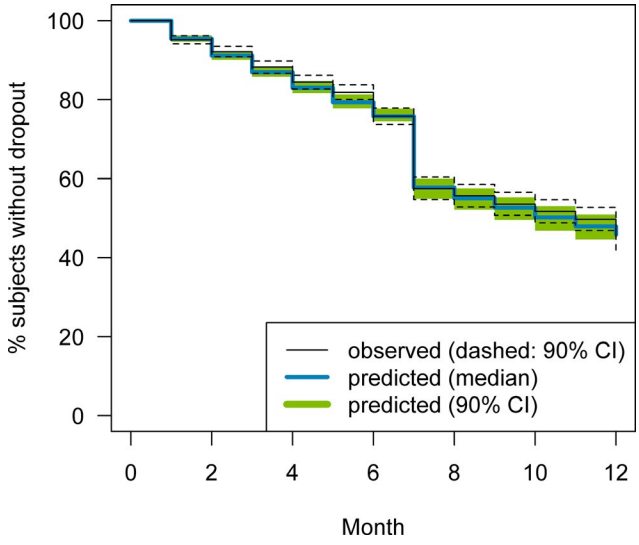

Figure 5 Observed and model-predicted percentages of patients remaining in the pivotal phase III studies over time. CI, confidence interval.

stratified by dose group in **Figure S4**) indicated that the observed data, including the variability, were well described with good predictive performance. Additional VPCs stratified by study are included in the **Supplementary Material** and also show a good predictive performance by study. The Kaplan–Meier plot (**Figure 5**) assessing the dropouts from the studies indicated close agreement between the model-predicted and the observed percentages of patients remaining in the study over time. A bootstrap analysis confirmed the robustness of the model and precision of the parameter estimation.

DISCUSSION

Elagolix is an oral nonpeptide GnRH antagonist developed for the management ofmoderate-to-severe pain associated with endometriosis and in combination with estradiol/norethindrone acetate for the magement of heavy menstrual bleeding associated with uterine leiomyomas (fibroids).[1,2,3] The relationships between elagolix exposures and clinical pain responses were characterized in the women with endometriosis with associated moderate-to-severe pain who participated in the two pivotal phase III studies and their extensions. A discrete-time Markov Chain model adequately described the relationship between elagolix exposure and DYS and NMPP response rates and adequately predicted patient dropouts over time with placebo and elagolix treatments.

A discrete-time Markov modeling approach was used for the current analysis as it has advantages for modeling composite end points that have dependence between successive observations, as well as dropouts.[10,12] In the current analysis, the DYS and NMPP responses were composites of reductions from baseline in pain scores plus changes in use of rescue analgesics. Directly modeling the binary composite end points by a Markov model instead of pain scores and rescue analgesics separately has the advantage of being able to directly compare with and predict the relevant study end point. In addition, the efficacy of elagolix in the phase III studies was assessed using two primary end points (percentage of patients with reductions in DYS and NMPP) rather than one. In cases where multiple end points are used, the question arises regarding how to model end point dependencies, as separate estimations of correlated end points do not fully leverage all the available date.[12] Thus, for the current analysis, two separate Markov models were built, which were linked by a correlated IIV term (eta) term, thereby allowing straightforward, interpretable inclusion of drug, and covariate effects. This modeling approach reduced the number of parameters compared with the full-state-approach while at the same time modeling correlation between end points, which enhanced the stability of the model and allowed for more sensitive detection of covariate relationships. This approach is also easily scalable in that it allows for modeling of multiple correlated end points simultaneously.

Pharmacodynamic Markov models are often built time-continuously, calculating transition rates by integrating over time. This allows for dynamic addition of drug effect from the pharmacokinetic profile and allows for use of observations occurring on an irregular schedule.[10,12] However, in the current analysis, the pain scores and analgesic use underlying the response end points were assessed daily, and the responder end points were subsequently calculated monthly (28 days). In our modeling, summarizing elagolix pharmacokinetics as a monthly average allowed for imputation in times of missing dosing information.

Although the discrete-time Markov modeling approach provided robust characterization of the exposure-efficacy relationships for elagolix, it should be noted that responder rates on DYS and NMPP were modeled, but not the pain scores. The decision to model responder rates was based on the phase III study designs, which identified responder rate as the primary end point, and took into account the fact that pain score alone does not account for patient use of analgesics; whereas, responder rate accounts for both a clinically meaningful reduction in pain score and analgesic use. In addition, not all patients in the extension studies were included in the analysis. Patients who received placebo in a pivotal study and subsequently received active treatment in an extension study were excluded from the extension study analyses, as their baseline pain scores were biased by the preceding placebo effect.

Experiencing DYS pain may depend on whether menstruation and/or ovulation has occurred or not. For instance, ovulation is a binary event and elagolix suppressed ovulation in a dose-dependent manner.[6] During the exposure-efficacy modeling, it was hypothesized that C_{avg} alone does not fully describe the probability of suppression, but that it is rather a combination with dose frequency (q.d. vs. b.i.d.) and a certain concentration limit that needs to be achieved. C_{trough} and continuous concentration-time profiles were also evaluated as alternative exposure metrics, but not found to be able to better characterize the observed DYS response. Part of the reason why this could not be further investigated is the big difference in daily dose between the two regimens that were investigated (200 mg b.i.d. corresponding to 400 mg

daily dose and 150 mg q.d. with 150 mg as daily dose). Therefore, as the exact reason could not be determined, the difference was captured by the dosing regimen effect (200 mg b.i.d. vs. 150 mg q.d.) parameter.

The current exposure-efficacy analysis in conjunction with exposure-safety analyses (manuscript under preparation) could provide important information for patients and clinicians (e.g., for selecting a suitable dosing regimen based on a comprehensive individualized utility assessment). Of the covariates evaluated for demographic characteristics, baseline hormone levels, disease severity measures, baseline analgesic use, and prior GnRH therapies, baseline DYS and NMPP scores were statistically significant for the respective placebo transition probabilities and age was statistically significant for the elagolix effect on NMPP response. Statistical significance of baseline DYS and NMPP scores could be explained by regression-to-the-mean effects or indicate that patients with higher baseline DYS and NMPP scores are sensitive to placebo effects. This could be due to the psychological impression of drug administration in blinded studies as baseline scores were not additionally statistically significant on the elagolix drug effect parameters, which were evaluated on EC_{50} values in the covariate testing procedure. Patients who were 10 years older than the median age (32 years) were predicted to have small increases in NMPP response rates (3–5.5%), although this is not believed to be clinically relevant. There were no statistically significant covariates for elagolix effect on DYS response rates. Based on these results, the selection of initial elagolix dose is not dependent on patient characteristics. Therefore, the lowest effective dose should be administered taking into account the treatment objectives in conjunction with safety and coexisting conditions as described in the label for the treatment of moderate to severe pain associated with endometriosis.[2]

Supporting Information. Supplementary information accompanies this paper on the *CPT: Pharmacometrics & Systems Pharmacology* website (www.psp-journal.com).

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Conflict of Interest. I.W., A.R.P., A.N., N.M.M., P.N., and J.N. are employees and shareholders of AbbVie.

Author Contributions. I.W. and A.R.P. wrote the manuscript. I.W., A.R.P., A.N., N.M.M., P.N., and J.N. designed the research. I.W., A.R.P., and A.N. performed the research. I.W. analyzed the data.

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