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ARTICLE

Effects of elagolix on the pharmacokinetics of omeprazole and its metabolites in healthy premenopausal women

Ahmed Nader[1,†] | **Nael M. Mostafa**[1] | **Elaine Kim**[2] | **Mohamad Shebley**[1]

[1]Clinical Pharmacology and Pharmacometrics, AbbVie Inc., North Chicago, Illinois, USA

[2]Regulated Bioanalysis, AbbVie Inc., North Chicago, Illinois, USA

Correspondence
Mohamad Shebley, Clinical Pharmacology and Pharmacometrics, Department R4PK, AbbVie Inc., Building AP31-3, 1 North Waukegan Road, North Chicago, IL 60064, USA.
Email: mohamad.shebley@abbvie.com

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Abstract

This study evaluated the effect of repeated doses of elagolix on the pharmacokinetics (PK) of omeprazole and its metabolites in healthy premenopausal female subjects. Adult premenopausal female subjects ($N = 20$) received a single oral dose of omeprazole (40 mg) on day 1 and day 11 and oral doses of elagolix (300 mg) twice-daily on days 3–11. Serial blood samples for assay of omeprazole and its metabolites were collected for 24 h after dosing on days 1 and 11. PK parameters were calculated for omeprazole, 5-hydroxyomeprazole and omeprazole sulfone; and were compared between day 1 and day 11. Pharmacogenetic testing was performed for CYP2C19 variant alleles and the results were used to compare the magnitude of elagolix–omeprazole drug–drug interaction (DDI) between the different genotype subgroups. Administration of elagolix 300 mg twice-daily for 9 days increased omeprazole exposure by 1.8-fold and decreased the metabolite-to-parent ratio for 5-hydroxyomeprazole by ~60%. Conversely, there was an increase in the metabolite-to-parent ratio for omeprazole sulfone by 25%. Elagolix increased omeprazole exposures by 2- to 2.5-fold in CYP2C19 extensive (EM) and intermediate (IM) metabolizer subjects, but decreased omeprazole exposures by 40% in poor metabolizer subjects. Exposures of 5-hydroxyomeprazole decreased by 20%–30% in all genotype subgroups, and omeprazole sulfone exposures increased by ~3-fold in EM and IM subjects. Elagolix is a weak inhibitor of CYP2C19 and exposure of CYP2C19 substrates may be increased upon coadministration with elagolix. Omeprazole may exhibit drug interactions due to multiple mechanisms other than CYP2C19-mediated metabolism; complicating the interpretation of results from omeprazole DDI studies.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Elagolix is an inhibitor of P-glycoprotein (P-gp) and a weak-to-moderate inducer of cytochrome P450 3A (CYP3A4). In vitro, elagolix was identified as a possible

[†]AbbVie was the affiliation of Dr. Nader at the time this research was conducted.

inhibitor of CYP2C19 with potential to increase plasma concentrations of drugs that are substrates of CYP2C19 if they are coadministered with elagolix.

WHAT QUESTION DID THIS STUDY ADDRESS?

What are the effects of elagolix on the pharmacokinetics of omeprazole and its metabolites in healthy subjects with different CYP2C19 genotypes and are P-gp and/or CYP3A4 potentially involved in the interaction between elagolix and omeprazole?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This study suggests that elagolix is a weak inhibitor of CYP2C19 and exposure of other CYP2C19 substrates may be increased upon coadministration with elagolix. These results also suggest P-gp, CYP3A4, and/or another unknown mechanism may also be potential mechanisms for drug interactions with omeprazole.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Future DDI studies with omeprazole as a CYP2C19 substrate should consider that omeprazole may exhibit complex drug interactions due to multiple mechanisms mediating metabolism and transport, which may confound the interpretation of study results.

INTRODUCTION

Elagolix is a novel, orally active, nonpeptide gonadotropin-releasing hormone (GnRH) receptor antagonist approved by the US Food and Drug Administration (FDA) for management of pain associated with endometriosis; and in combination with estradiol (E2) and norethindrone acetate (NETA) for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids).[1–4] Elagolix inhibits the secretion of gonadotropins (follicle-stimulating hormone [FSH] and luteinizing hormone [LH]) leading to the suppression of ovarian E2 and progesterone (P) secretion. Elagolix inhibits these gonadotropins in a dose-dependent manner, increasing the likelihood of achieving an acceptable balance between therapeutic efficacy and unwanted adverse effects.[5,6] Elagolix also provides advantages over GnRH agonists in that it has a rapid onset of action, is orally bioavailable, does not produce a flare effect, and has the option of being promptly discontinued if necessary.[5,7,8]

The pharmacokinetic (PK) profile of elagolix has been well-characterized in several phase I studies. Elagolix is rapidly absorbed after oral dosing, reaching maximum concentrations at 1.0–1.5 h, and has a half-life of 4–6 h. It shows linear PK and minimal or no accumulation upon multiple dosing with once or twice daily regimens.[5] Elagolix doses of 150 mg once daily or 200 mg twice daily were tested in phase III studies for the treatment of endometriosis with associated pain; efficacy and safety of elagolix as a therapy for endometriosis with associated pain has been demonstrated by data from phase II and phase III trials.[2,9] Elagolix (300 mg) in combination with estradiol (1 mg) and norethindrone acetate (0.5 mg) demonstrated efficacy for the treatment of heavy menstrual bleeding associated with uterine fibroids in phase III clinical trials.[4,10,11]

Elagolix is a substrate of cytochrome P450 3A (CYP3A), P-glycoprotein (P-gp) efflux transporter, and organic anion transporting polypeptide 1B1 (OATP1B1) uptake transporter.[3,6] Drug–drug interaction (DDI) studies with midazolam and digoxin demonstrated that elagolix is a weak to moderate inducer of CYP3A (in vivo reduced midazolam exposures; in vitro maximum induction 20-fold)[3,12,13] and an inhibitor of P-gp (in vivo increased digoxin exposures; in vitro IC50 54 μM).[3,12-14] Additionally, in vitro CYP inhibition experiments have shown that elagolix may be an inhibitor of CYP2C19 (in vitro K_I 34 μM, k_{inact} 0.029 min^{-1}) with potential to increase plasma concentrations of drugs that are substrates of CYP2C19 if these drugs are coadministered with elagolix.[3,12,13]

Omeprazole is a widely used proton-pump inhibitor and a sensitive probe substrate for CYP2C19-mediated metabolism. It is metabolized via multiple pathways with CYP2C19-mediated formation of 5-hydroxyomeprazole and CYP3A-mediated formation of omeprazole sulfone being the main pathways responsible for omeprazole elimination.[15–18] Based on its relative selectivity and sensitivity to changes in CYP2C19 enzyme activity, it is currently recommended by US FDA for assessment of effects of coadministered drugs or compounds on the activity of CYP2C19.[19]

The objective of this study was to evaluate the effect of multiple doses of elagolix on the PK of omeprazole and its metabolites using a single-arm study design in adult healthy premenopausal female subjects.

METHODS

The protocol was approved by the institutional review board at the study site (Vista Medical Center East Institutional Review Board, Waukegan, IL, USA) and each participant provided written informed consent prior to his or her participation in the study. The study was conducted in accordance with the protocol, International Council for Harmonisation (ICH) Good Clinical Practice guidelines, applicable regulations and guidelines governing clinical study conduct, and ethical principles that have their origin in the Declaration of Helsinki.

Study design and participants

This was a single-center, multiple-dose, open-label, single-arm study designed to assess the effect of elagolix on the PK of omeprazole and its metabolites (5-hydroxyomeprazole and omeprazole sulfone) in healthy premenopausal female subjects ($N = 20$) between 18 and 49 years of age, inclusive. Subjects received a single oral dose of omeprazole 40 mg under fasting conditions on day 1 as shown in (Figure S1). Beginning on day 3, subjects received elagolix 300 mg b.i.d. under fasting conditions every day until day 10. The morning dose was administered after an overnight fast, while the afternoon dose was administered approximately 2 h after a meal and no food was consumed for 1 h after dosing. On day 11, subjects received elagolix 300 mg b.i.d. and a single dose of omeprazole 40 mg in the morning under fasting conditions. Doses of elagolix were separated by approximately 12 h.

Subjects were confined to the study site and supervised for approximately 13 days. Confinement began on day −1 and ended after the collection of the 24-h blood samples and completion of scheduled study procedures on day 12. Subjects returned to the study site at 14 days (±3 days) after the last dose of study drug for the follow-up visit.

PK sampling and bioanalytical methods

Blood samples for omeprazole, 5-hydroxyomeprazole, and omeprazole sulfone assays were collected into dipotassium ethylenediaminetetracetic acid (K_2EDTA)-containing collection tubes prior to dosing (0 h) and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 24 h after dosing on days 1 and 11. Blood samples for elagolix assay were collected into K_2EDTA-containing collection tubes prior to dosing (0 h) and at 0.5, 1, 1.5 and 2 h after the morning dose on day 11.

Plasma concentrations of elagolix were determined using a salt-assisted protein precipitation extraction and a validated liquid chromatography method with tandem mass spectrometry (MS/MS) detection by the Drug Analysis Department at AbbVie (North Chicago, IL, USA) as previously described.[20] The lower limit of quantification (LLOQ) for elagolix was established at 1.57 ng/ml. Samples quantified below the LLOQ were reported as zero. Plasma concentrations for omeprazole, 5 hydroxyomeprazole, and omeprazole sulfone were determined using a validated liquid chromatography method with MS/MS detection by PPD (Middleton, WI, USA).

For the omeprazole, 5-hydroxyomeprazole, and omeprazole sulfone assays, the analytes of interest (omeprazole, 5-hydroxyomeprazole, and omeprazole sulfone) were extracted by protein precipitation from a sample volume of 50 μl. Chromatographic separation for omeprazole, 5-hydroxyomeprazole, omeprazole sulfone, and their internal standards was achieved using a Thermo, Aquasil C18, 100 × 2.1 mm, 5 μ column and a gradient condition with a mobile phase A of 10% acetic acid (aq.)/10% ammonium acetate (aq.)/water (0.5/0.2/99.3 (v/v/v)) and a mobile phase B of acetonitrile/methanol/10% acetic acid (aq.)/10% ammonium acetate (aq.)/water (45/45/0.5/0.2/9.3 (v/v/v/v/v)). A Waters Xevo TQ-S mass spectrometer employing electrospray ionization in positive ion mode was used to monitor the analytes for omeprazole, 5-hydroxyomeprazole, omeprazole sulfone, and their internal standards. For omeprazole, 5 hydroxyomeprazole, and omeprazole sulfone, the lower limit of quantification (calibration range) was 1.00 ng/ml (1.00–1000 ng/ml) for each analyte.

Multiple-reaction monitoring (MRM) transitions were m/z 346.3 → 198.3 for omeprazole, m/z 349.3 → 198.3 for the internal standard omeprazole-d3, m/z 362.3 → 214.4 for 5-hydroxyomeprazole, m/z 365.2 → 214.2 for the internal standard 5-hydroxyomeprazole-d3, m/z 362.3 → 298.5 for omeprazole sulfone, and m/z 365.3 → 301.6 for the internal standard omeprazole sulfone-d3. The inter-assay precision and accuracy/bias as demonstrated by the performance of the quality control samples were ≤7.35% and between −3.89% and 1.61% for omeprazole, ≤10.9% and between 0.282% and 5.99% for 5-hydroxyomeprazole, and ≤13.0% and between −1.74% and 5.75% for omeprazole sulfone, respectively.

Pharmacogenetic testing for CYP2C19 genetic polymorphisms

Testing was performed for CYP2C19 variants including the *2 (rs4244285), *3 (rs4986893), *4 (rs28399504), *8

(rs41291556), and *10 (rs6413438) alleles. Pyrosequencing (PSQ) genotyping assays were developed for these variant positions using the PyroMark Assay Design Software v2.0 (Qiagen Inc., Germantown, MD, USA). Primers selected for the PSQ assays were in-silico screened for polymorphisms within the priming and sequencing regions of the genome using the UCSC browser[21] and SNPcheck (Certus Technology Associates Limited and EMQN c/o Manchester Centre for Genomic Medicine). Genomic DNA amplification reactions were processed for the assay as described by the manufacturer in the Pyrosequencing Lab Instructions – MD and analyzed using the Pyrosequencer 96 MD instrument and software (Qiagen, Inc. Germantown, MD, USA).

The results of the CYP2C19 genetic polymorphism testing were used to evaluate the impact of CYP2C19 polymorphism on the PK of omeprazole and its metabolites. In addition, the magnitude of elagolix–omeprazole DDI was compared between the different subject subgroups based on CYP2C19 metabolizer status (extensive metabolizer "EM", intermediate metabolizer "IM", or poor metabolizer "PM").

PK and statistical analyses

Plasma concentrations of elagolix were summarized and compared to those previously observed[5] in healthy subjects receiving the 300 mg b.i.d. dosing regimen to confirm achievement of adequate elagolix exposures for assessment of the DDI potential. PK parameters for omeprazole, 5-hydroxyomeprazole, and omeprazole sulfone were estimated using noncompartmental analyses (NCA) in Phoenix WinNonLin (Certara, Princeton, NJ, USA). Individual PK parameters included the observed maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), area under the plasma concentration–time curve (AUC) calculated using the trapezoidal rule up to the last measurable concentration (AUC_t) and from time 0 to infinity (AUC_{inf}), as well as the terminal phase elimination half-life ($t_{1/2}$). Additionally, the metabolite-to-parent (M:P) AUC ratios were calculated for both metabolites compared to omeprazole.

Statistical analyses were conducted using SAS Version 9.3 (SAS Institute, Cary, NC, USA). To assess the effect of elagolix on omeprazole, a repeated measures analysis was performed for omeprazole and its metabolites on the natural logarithms of C_{max} and AUC utilizing data from day 1 (omeprazole alone) and day 11 (omeprazole in combination with elagolix). The 90% confidence intervals were obtained for ratio estimates by taking the anti-logarithm of the upper and lower limits of confidence intervals for the difference of the least squared means on the logarithmic scale obtained within the framework of the repeated measures analysis model. Similar analyses were conducted for the M:P AUC ratios for 5-hydroxyomeprazole and omeprazole sulfone.

Safety assessments

Safety was evaluated during confinement and at each study visit through adverse event monitoring, vital signs measurements, physical examinations, and routine laboratory tests.

RESULTS

Participants and demographics

Twenty adult premenopausal female subjects were enrolled in and completed the study (Table S1). The mean age was 37.9 years (range 26–48 years) and the mean body mass index was 27.2 kg/m^2 (range 20.1–29.9 kg/m^2).

PK of elagolix, omeprazole and omeprazole metabolites

Although the study was designed to only assess the effects of elagolix on omeprazole, elagolix concentrations were measured to ensure achievement of adequate exposures for assessment of the DDI potential. Mean (SD) elagolix C_{max} on day 11 following 300 mg b.i.d. dosing was 1410 ng/ml (519); which is comparable to previously observed exposures (C_{max}: 1479 (740)) under the same dosing regimen[5]; indicating appropriateness for DDI assessment.

The mean (SD) plasma concentration–time profiles and PK parameters of omeprazole and its metabolites when omeprazole was administered alone and in the presence of elagolix are shown in Figure 1 and Table 1, respectively.

Omeprazole exposures were increased on day 11 compared to day 1 and the effect was most pronounced during the early timepoints (increased C_{max} and AUC) compared to the terminal elimination phase. Elagolix 300 mg b.i.d. dosing increased omeprazole C_{max} by 1.9-fold and AUC_{inf} by 1.8-fold (Figure 2). Conversely, omeprazole terminal elimination half-life and T_{max} were unchanged on day 11 compared to day 1 (Table 1).

Similar to omeprazole, results for omeprazole sulfone showed that exposures were increased on day 11 compared to day 1; with the effect most pronounced for C_{max} and AUC (increased C_{max} by 2.7-fold and AUC_{inf} by 2.5-fold; Figure 2) and relatively unchanged terminal elimination half-life and T_{max} for omeprazole sulfone on day 11 compared to day 1 (Table 1).

Conversely, 5-hydroxyomeprazole exposures were decreased on day 11 compared to day 1 (C_{max} decreased by approximately 30% and AUC_{inf} decreased by 25%; Figure 2), although the terminal elimination half-life was

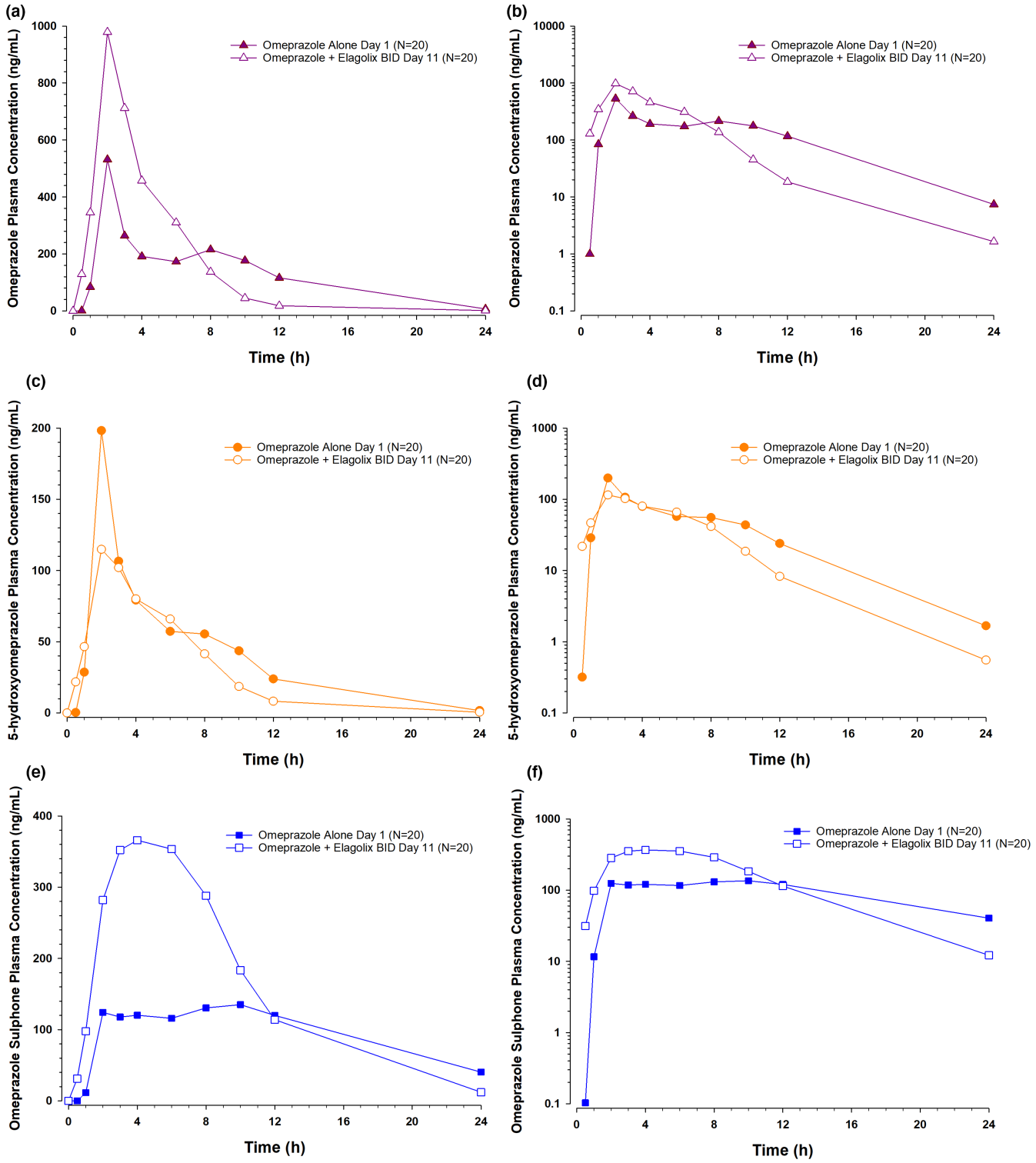

FIGURE 1 Mean plasma concentration–time profiles for omeprazole (a, b), 5-hydroxyomeprazole (c, d), and omeprazole sulfone (e, f) when omeprazole is dosed alone (filled shapes) or with elagolix (open shapes) Profiles shown on linear scale (a, c, e) or log-linear scale (b, d, f). b.i.d., twice daily

unchanged. Furthermore, elagolix 300 mg b.i.d. dosing, seemed to increase the T_{max} of 5-hydroxyomeprazole by 1 h (Table 1).

The apparent terminal phase elimination rate constant could not be calculated for omeprazole for one subject on day 1, and for omeprazole sulfone for three subjects on day 1. Therefore, the ratio of 5-hydroxyomeprazole to omeprazole AUC_{inf} for one subject on day 1 and the ratio of omeprazole sulfone to omeprazole AUC_{inf} for four subjects on day 1 could not be calculated.

TABLE 1 Geometric mean (mean, percentage coefficient of variation) pharmacokinetic parameters of omeprazole and its metabolites

Pharmacokinetic parameter	(Units)	Study day 1 Omeprazole 40 mg (*N* = 20)	Study day 11 Omeprazole 40 mg + elagolix 300 mg b.i.d. (*N* = 20)
Omeprazole			
C_{max}	(ng/ml)	491 (717, 88)	956 (1130, 47)
T_{max}[a]	(h)	2.0 (2.0–10)	2.0 (1.0–8.0)
AUC_t	(ng•h/ml)	1820 (3070, 113)	3320 (3760, 44)
AUC_{inf}	(ng•h/ml)	1880 (3200, 113)[c]	3360 (3790, 44)
$t_{1/2}$[b]	(h)	1.57 (0.773)[c]	1.65 (0.939)
5-Hydroxyomeprazole			
C_{max}	(ng/ml)	195 (238, 61)	134 (142, 34)
T_{max}[a]	(h)	2.0 (2.0–10)	3.0 (1.0–8.0)
AUC_t	(ng•h/ml)	857 (911, 35)	643 (659, 22)
AUC_{inf}	(ng•h/ml)	883 (932, 33)	664 (679, 21)
$t_{1/2}$[b]	(h)	1.88 (0.794)	1.97 (0.901)
$RAUC_t$[a]		0.65 (0.044–2.1)	0.20 (0.071–0.84)
$RAUC_{inf}$[a]		0.61 (0.048–2.3)[c]	0.20 (0.071–0.90)
Omeprazole sulfone			
C_{max}	(ng/ml)	152 (219, 78)	411 (458, 31)
T_{max}[a]	(h)	3.5 (2.0–12)	4.0 (3.0–8.0)
AUC_t	(ng•h/ml)	1240 (2250, 104)	3380 (3780, 37)
AUC_{inf}	(ng•h/ml)	1400 (2100, 107)[d]	3450 (3860, 38)
$t_{1/2}$[b]	(h)	3.27 (1.59)[d]	3.30 (0.821)
$RAUC_t$[a]		0.76 (0.13–1.1)	0.97 (0.67–1.5)
$RAUC_{inf}$[a]		0.85 (0.52–1.1)[e]	0.99 (0.71–1.5)

Abbreviations: C_{max}, maximum plasma concentration; $RAUC_{inf}$, metabolite-to-omeprazole area under curve from time 0 to infinity (AUC_{inf}) ratio; $RAUC_t$, metabolite-to-omeprazole last measurable concentration (AUC_t) ratio; $t_{1/2}$, elimination half-life; T_{max}, time to C_{max}.

[a]Median (minimum–maximum).

[b]Harmonic mean (pseudo-standard deviation).

[c]*N* = 19.

[d]*N* = 17.

[e]*N* = 16.

For the M:P AUC ratios, the central value ratios as well as the point estimates and 90% confidence intervals for the day 11 versus day 1 comparison are presented in Table 2. The M:P AUC ratio for 5-hydroxyomeprazole was decreased by approximately 60%; while the corresponding ratio for omeprazole sulfone was increased by 25%.

Impact of CYP2C19 genetic polymorphisms on the PK of omeprazole and its metabolites

The raw CYP2C19 allelic variant data were interpreted for the individual genotype calls by the Pyromark MD software. After tabulating the data for each subject, a CYP2C19 functional status call was generated using rules based on the functional impact of each variant allele. The functional impact was derived from the literature which is summarized within the Pharmacogene Variation Consortium web pages (www.pharmvar.org).[22] Of the variants tested, *2, *3, *4, and *8 are considered nonfunctional or poor metabolizer (PM) alleles and are key drivers of this phenotype. A subject that was homozygous for any of the listed PM alleles was considered to have a PM status and those who were heterozygous for a PM allele were considered to have decreased function or an intermediate metabolizer (IM) status. Subjects with no PM alleles expressed were considered to have extensive metabolizer (EM) status for CYP2C19.

Twelve subjects were EM for CYP2C19, five were IM, and three were PM. The impact of elagolix dosing on the PK of omeprazole and its metabolites was compared

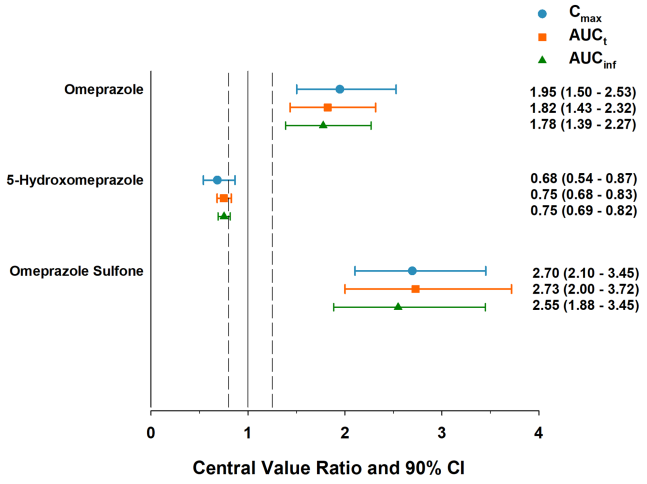

FIGURE 2 Point estimates and 90% confidence intervals (CIs) for maximum plasma concentration (C_{max}) and area under curve (AUC) ratios of omeprazole, 5-hydroxyomeprazole, and omeprazole sulfone on day 11 compared to day 1. Dashed vertical lines represent central value ratios of 0.8 and 1.25

between the CYP2C19 EM, IM, and PM subjects to provide additional understanding of the impact on the different metabolic pathways involved in omeprazole metabolism (Figures 3–5). Changes in omeprazole and metabolite exposures in EM subjects were consistent with those observed in the overall group (i.e., all study subjects combined). Elagolix increased AUC_{inf} for omeprazole and omeprazole sulfone by 2-fold and 2.7-fold, respectively, and decreased 5-hydroxyomeprazole AUC_{inf} by 23%. Similar changes were also observed in IM subjects, although with a slightly larger magnitude (AUC_{inf} for omeprazole and omeprazole sulfone increased by 2.6-fold and 3-fold, respectively, and for 5-hydroxyomeprazole decreased by 30%). In both EM and IM subjects, similar changes were observed for C_{max} compared to AUC_{inf} for all three analytes.

In PM subjects, elagolix decreased AUC_{inf} for omeprazole and 5-hydroxyomeprazole by 40% and 20%, respectively, while C_{max} was increased for both analytes by 23%–33%. Omeprazole sulfone C_{max} was unchanged after elagolix dosing. An AUC_{inf} comparison using central value ratio and 90% confidence interval was not completed for omeprazole sulfone in PM subjects since AUC_{inf} values for both day 1 and day 11 were only available from one subject due to inability to estimate half-life on day 1 for the other two subjects. AUC_{inf} on day 11 for that subject was 40% lower compared to the corresponding AUC_{inf} on day 1. Furthermore, T_{max} was decreased in all three subjects on day 11 compared to day 1 (2 vs. 8 h, 2 vs. 10 h, and 1 vs. 2 h).

Safety

The regimens tested were generally well tolerated by the subjects in this study. Six subjects had treatment-emergent adverse events (i.e., dysmenorrhea, irregular menstruation, hot flush) that were assessed by the investigator as having a reasonable possibility of being related to elagolix. All adverse events were mild or moderate in severity and none led to discontinuation of the study drug. No clinically significant vital signs, electrocardiograms, physical examinations, or laboratory measurements were observed during the study.

DISCUSSION

In this DDI study, the effects of elagolix 300 mg b.i.d. dosing on the PK of a single dose of omeprazole, a sensitive CYP2C19 substrate, and its metabolites was evaluated based on in vitro data suggesting elagolix may be an inhibitor of CYP2C19 enzyme. Following administration of elagolix 300 mg b.i.d. for 9 days, omeprazole exposure increased by 1.8-fold (primarily driven by the increase in EM subjects); indicating that elagolix is a weak inhibitor of CYP2C19 and that coadministration of elagolix with other

TABLE 2 Comparison of metabolite-to-parent area under curve (AUC) ratios for omeprazole and its metabolites with/without elagolix coadministration

Regimens test vs. reference	Pharmacokinetic parameter	Central value		Relative bioavailability	
		Day 11	Day 1	Point estimate	90% CI
5-Hydroxomeprazole:omeprazole					
Day 11 vs. day 1	M:P AUC_t ratio	0.194	0.471	0.412	0.326, 0.520
	M:P AUC_{inf} ratio	0.198	0.458	0.432	0.343, 0.544
Omeprazole sulfone:omeprazole					
Day 11 vs. day 1	M:P AUC_t ratio	1.017	0.679	1.497	1.272, 1.761
	M:P AUC_{inf} ratio	1.028	0.825	1.246	1.092, 1.422

Note: Study day 1: omeprazole 40 mg (reference), Study day 11: elagolix 300 mg b.i.d. + omeprazole 40 mg (test).

Abbreviations: AUC_{inf}, area under curve from time 0 to infinity; AUC_t, AUC to last measurable concentration; CI, confidence interval; M:P, metabolite:parent.

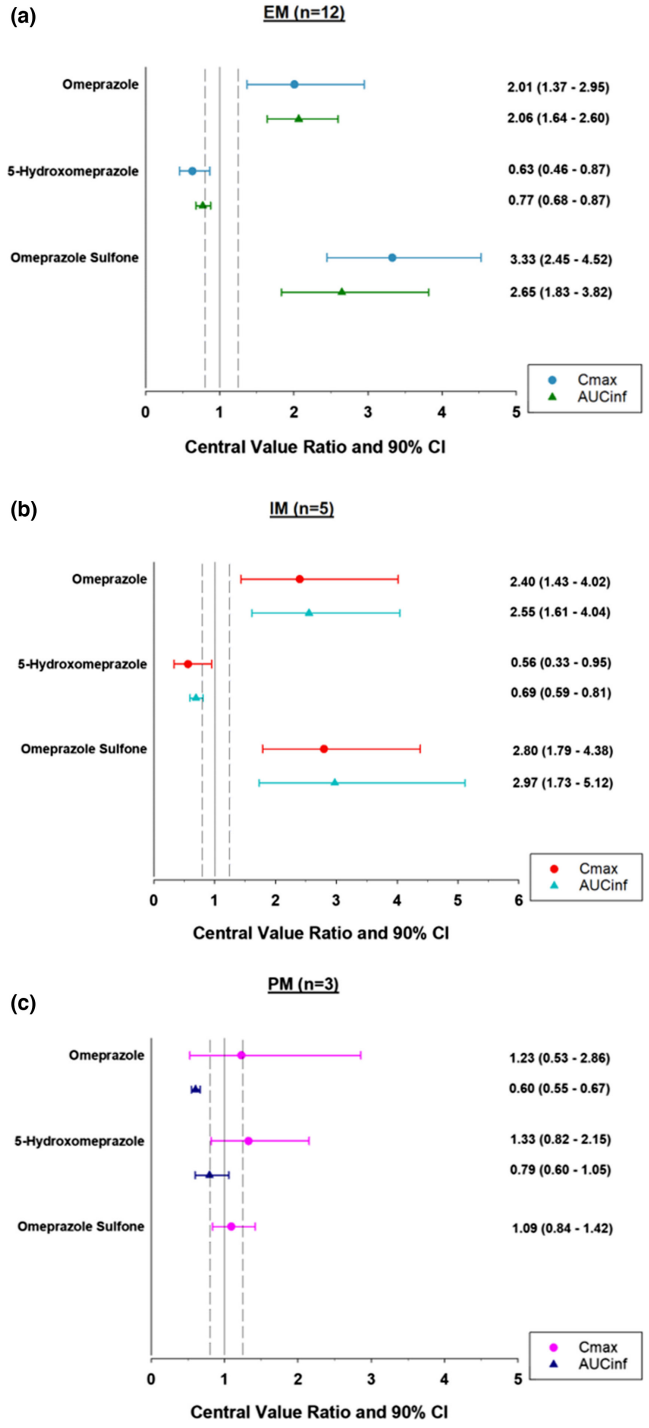

FIGURE 3 Point estimates and 90% confidence intervals (CIs) for maximum plasma concentration (C_{max}) and area under curve (AUC) ratios of omeprazole, 5-hydroxyomeprazole, and omeprazole sulfone on day 11 compared to day 1 by CYP2C19 genotype status. (a) Extensive metabolizers (EM). (b) Intermediate metabolizers (IM). (c) Poor metabolizers (PM). Dashed vertical lines represent central value ratios of 0.8 and 1.25

substrates of CYP2C19 may increase plasma concentrations of these drugs.[3] Given that omeprazole is not solely eliminated through CYP2C19-mediated metabolism, the evaluation of 5-hydroxyomeprazole and omeprazole sulfone PK as well as the effects of CYP2C19 genotype were included to provide further insights into the mechanism of DDI between elagolix and omeprazole.

Omeprazole is primarily metabolized via CYP2C19-mediated hydroxylation to 5-hydroxyomeprazole. Several studies have also reported CYP3A4-mediated omeprazole sulfoxidation to the sulfone metabolite[23–25] with 5-hydroxyomeprazole and omeprazole sulfone being the two primary metabolites detected in plasma.[17,26] In addition, CYP3A4 and CYP2C19 metabolism is considered the primary route of elimination for 5-hydroxyomeprazole and omeprazole sulfone, respectively.[27] Hence, the impact on omeprazole and metabolite PK from drugs that affect both CYP2C19 and CYP3A4 expression or function is complex and could be more challenging to predict or interpret.

In addition, recent evidence suggests that efflux transporters may be involved in the absorption of omeprazole. Omeprazole low aqueous solubility and high permeability resemble a Biopharmacuetics Classification System (BCS) Class 2 drug.[28] For BCS class 2 drugs, efflux transporters may have a significant impact on absorption from the gastrointestinal tract after oral administration.[29] An in vitro study reported that P-glycoprotein (P-gp) efflux transporter may be involved in the transport of omeprazole across Caco-2 cells.[30] An in vivo study in rabbits demonstrated an increase in omeprazole C_{max} and AUC of more than 2-fold upon coadministration with the P-gp inhibitor verapamil.[31]

Similar evidence has also been reported in humans in a developmental pharmacogenetics study of omeprazole PK in neonates and young infants.[32] Population PK modeling results from that study showed that the omeprazole model-estimated absorption rate constant was 7-fold and 2-fold higher in subjects homozygous and heterozygous for ABCB1 (gene expressing P-gp) mutant alleles, respectively, compared to subjects who were homozygous for the wild-type allele.[32] Based on these results, an increase in omeprazole absorption may be expected in subjects with reduced intestinal P-gp efflux function. Overall, current evidence suggests that omeprazole PK are sensitive to changes in CYP2C19 activity, and may also be affected by other metabolic or transporter pathways such as CYP3A4 or P-gp. However, there is a limitation in the hypothesis of P-gp involvement in omeprazole absorption and DDI with elagolix, such as that the in vitro Caco-2, in vivo rabbit and neonates pharmacogenetics studies only point towards possibility of P-gp or other efflux transporters involvement, but not a definitive involvement or significant contribution of P-gp to omeprazole in vivo disposition in adults. In addition, the absolute oral bioavailability of omeprazole is 30%–40%, with an estimated fraction absorbed and escaping intestinal first pass (fa*fg) of approximately

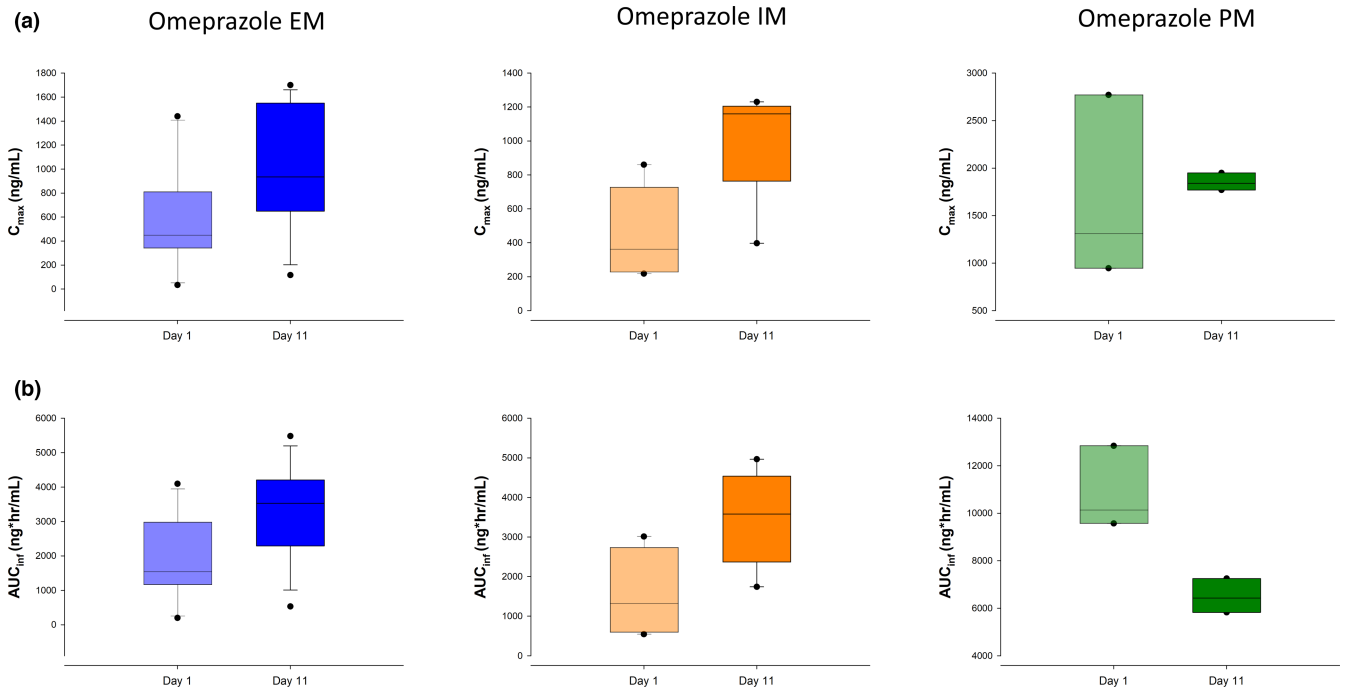

FIGURE 4 Changes in omeprazole (a) maximum plasma concentration (C_{max}) and (b) area under curve from time 0 to infinity (AUC_{inf}) between day 1 (omeprazole alone) and day 11 (coadministration with elagolix) by CYP2C19 genotype status. Box plot shown as median with 25th to 75th percentiles and whiskers represent 10th and 90th percentiles. EM, extensive metabolizers; IM, intermediate metabolizers; PM, poor metabolizers

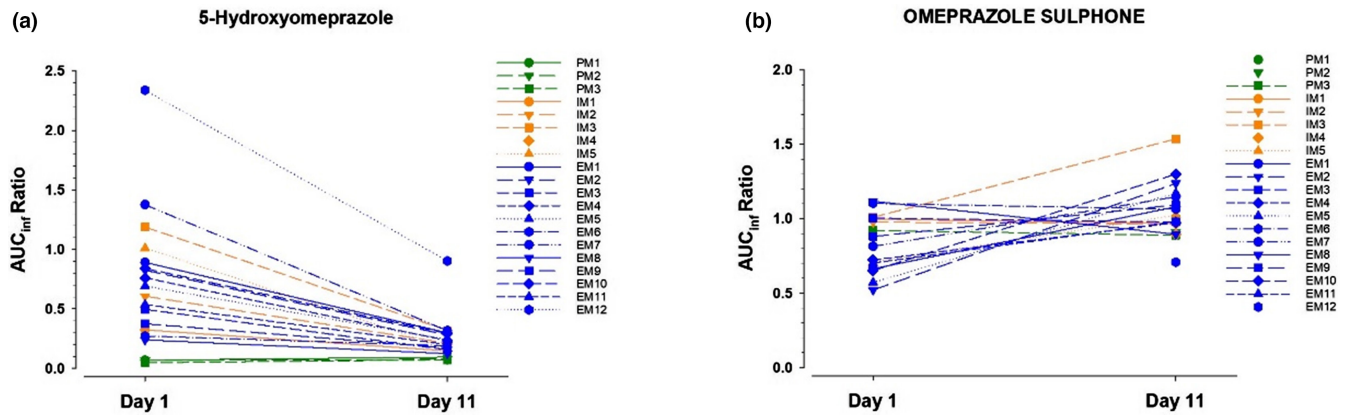

FIGURE 5 Changes in metabolite:parent area under curve from time 0 to infinity (AUC_{inf}) ratio for (a) 5-hydroxyomeprazole and (b) omeprazole sulfone between day 1 and day 11 by CYP2C19 genotype status

0.80, suggesting a relatively high absorption and limited contribution of gut efflux transport or metabolism.

Elagolix is a weak to moderate inducer of CYP3A4 based on dose-dependent changes in midazolam exposures following dosing with different elagolix dosing regimens. Elagolix 150 mg q.d. and 300 mg b.i.d. dosing regimens resulted in reductions in midazolam AUC by 35% and 54% respectively.[3,14] Elagolix is also an inhibitor of P-gp based on results from a DDI study with digoxin in which digoxin C_{max} and AUC was increased by 71% and 26%, respectively, upon administration following an elagolix 200 mg b.i.d. regimen.[3] In addition to effects on CYP2C19, the results of the current DDI study with omeprazole were investigated to explore whether elagolix effects on CYP3A4 and/or P-gp could have contributed to the observed study results.

Elagolix 300 mg b.i.d. dosing decreased 5-hydroxyomeprazole exposures by 25% and decreased the M:P AUC ratio for this metabolite by approximately 60%. These results are consistent with inhibition of CYP2C19-mediated formation of 5-hydroxyomeprazole. However, this reduction in CYP2C19-mediated omeprazole

clearance was not associated with a change in omeprazole half-life. This could be either due to a DDI effect that is occurring primarily during first-pass through the intestine and the liver or due to shifting of omeprazole clearance to non-CYP2C19-mediated pathways. The observed increase in omeprazole C_{max} and reduction in 5-hydroxyomeprazole C_{max} may suggest a DDI effect during first-pass. However, it is difficult to conclude whether such an increase in omeprazole bioavailability was due to CYP2C19 inhibition only or a combined effect of CYP2C19 and intestinal efflux transporters (i.e., P-gp) inhibition, or potentially another unknown mechanism. A shift in omeprazole clearance to non-CYP2C19-mediated pathway(s) can be inferred from the increase in omeprazole sulfone exposures by 2.6-fold following elagolix dosing. Such an increase may be driven by a shift of omeprazole clearance to CYP3A4-mediated pathways together with possible induction of CYP3A4 function by elagolix. The latter is suggested from the observed increase in omeprazole sulfone M:P AUC ratio by 25%−50% following elagolix dosing.

Investigation of the effects of elagolix on omeprazole and metabolite PK in the different CYP2C19 genotype subgroups provided additional insights into potential mechanisms involved in the interaction. Results in EM and IM subjects were generally consistent with those observed in the overall study population given the relatively functional CYP2C19 metabolism in both groups. However, in PM subjects an increase in omeprazole C_{max} by 23% and a reduction in AUC by 40% were observed. In addition, there was a marked reduction in omeprazole T_{max} in all three PM subjects; indicating faster absorption upon administration following elagolix dosing. Although definitive conclusions cannot be drawn given the small number of PM subjects, these results may suggest a more pronounced interaction via a net inhibition of an absorption mechanism or intestinal efflux transporter (i.e., higher C_{max} and shorter T_{max} due to P-gp inhibition) and induction of CYP3A4 (i.e., lower AUC due to CYP3A4 induction) in the absence of significant CYP2C19 activity in PM subjects. Changes in 5-hydroxyomeprazole exposures in PM subjects on day 11 mirrored changes in omeprazole with no notable increase in M:P AUC ratio in any of the three subjects, confirming minimal CYP2C19 activity in those subjects and potentially a minor contribution from CYP3A metabolism.[33]

One limitation of this study is the small number of PM subjects enrolled in the study. Although the study was adequately powered to detect a DDI between elagolix and omeprazole, it was not designed to prospectively enroll enough subjects in each CYP2C19 genotype group. Future DDI studies with larger sample size of PM subjects and drugs that may affect the multiple mechanisms involved in omeprazole disposition may confirm observations from this study. Additionally, the current DDI study did not include evaluation of P-gp polymorphisms since it was not hypothesized a priori at the time of conducting the study that P-gp would have a significant impact on omeprazole PK. However, the results of this study as well as cited literature are hypothesis-generating and encourage future research into the effects of P-gp or other efflux transporters on omeprazole disposition. Only NCA were conducted for this study, and additional analyses using empirical or physiologically based models are being investigated and may provide additional insights into the possible mechanisms involved in DDI between elagolix and omeprazole.

CONCLUSIONS

The results of this study suggest that elagolix is a weak inhibitor of CYP2C19 based on FDA criteria for clinical CYP enzyme inhibitors[34] and that exposure of other CYP2C19 substrates may be increased upon coadministration with elagolix. Omeprazole may exhibit complex drug interactions due to multiple mechanisms including CYP2C19- and CYP3A4-mediated metabolism and transport mediated by P-gp or another unknown mechanism. Future DDI studies with omeprazole as a CYP2C19 substrate should take into consideration potential confounding from additional mechanisms in the interpretation of study results. Alternatively, additional research to identify more selective CYP2C19 substrates may be warranted for future use in clinical DDI studies.

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CONFLICT OF INTEREST

N.M.M, E.K., and M.S. are employees of AbbVie and may hold AbbVie stock or stock options. A.N. is a former employee of AbbVie and may hold stock or stock options. This work was supported by AbbVie Inc. AbbVie contributed to the study design, research, and interpretation of data, and the writing, review, and approval of the publication.

AUTHOR CONTRIBUTIONS

A.N., N.M.M., E.K., and M.S. wrote the manuscript. A.N., N.M.M., and M.S. designed the research. A.N., N.M.M.,

E.K., and M.S performed the research. A.N., N.M.M., and M.S. analyzed the data.

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