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## ORIGINAL STUDY

# Efficacy and safety of elinzanetant, a selective neurokinin-1,3 receptor antagonist for vasomotor symptoms: a dose-finding clinical trial (SWITCH-1)

James A. Simon, MD,<sup>1</sup> Richard A. Anderson, MD,<sup>2</sup> Elizabeth Ballantyne, BSc,<sup>3</sup> James Bolognese, MStat,<sup>4</sup> Cecilia Caetano, MD,<sup>5</sup> Hadine Joffe, MD,<sup>6</sup> Mary Kerr, PhD,<sup>3</sup> Nick Panay, FRCOG,<sup>7</sup> Christian Seitz, MD,<sup>8</sup> Susan Seymore, BSc,<sup>3</sup> Mike Trower, PhD,<sup>3</sup> Lineke Zuurman, MD,<sup>5</sup> and Steve Pawsey, MB BS<sup>3</sup>

### Abstract

**Objective:** Neurokinin (NK)-3 and NK-1 receptors have been implicated in the etiology of vasomotor symptoms (VMS) and sleep disturbances associated with menopause. This phase 2b, adaptive, dose-range finding study aimed to assess the efficacy and safety of multiple doses of elinzanetant (NT-814), a selective NK-1,3 receptor antagonist, in women experiencing VMS associated with menopause, and investigate the impact of elinzanetant on sleep and quality of life.

**Methods:** Postmenopausal women aged 40 to 65 years who experienced seven or more moderate-to-severe VMS per day were randomized to receive elinzanetant 40, 80, 120, or 160 mg or placebo once daily using an adaptive design algorithm. Coprimary endpoints were reduction in mean frequency and severity of moderate-to-severe VMS at weeks 4 and 12. Secondary endpoints included patient-reported assessments of sleep and quality of life.

**Results:** Elinzanetant 120 mg and 160 mg achieved reductions in VMS frequency versus placebo from week 1 throughout 12 weeks of treatment. Least square mean reductions were statistically significant versus placebo at both primary endpoint time points for elinzanetant 120 mg (week 4:  $-3.93$  [SE, 1.02],  $P < 0.001$ ; week 12:  $-2.95$  [1.15],  $P = 0.01$ ) and at week 4 for elinzanetant 160 mg ( $-2.63$  [1.03];  $P = 0.01$ ). Both doses also led to clinically meaningful improvements in measures of sleep and quality of life. All doses of elinzanetant were well tolerated.

**Conclusions:** Elinzanetant is an effective and well-tolerated nonhormone treatment option for postmenopausal women with VMS and associated sleep disturbance. Elinzanetant also improves quality of life in women with VMS.

**Key Words:** KNDy neuron – Menopause – Neurokinin B – Neurokinin-1,3 receptor antagonist – Substance P – Vasomotor symptoms.

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From the <sup>1</sup>George Washington University, IntimMedicine Specialists, Washington, DC; <sup>2</sup>MRC Centre for Reproductive Health, Queens Medical Research Institute, University of Edinburgh, Edinburgh, United Kingdom; <sup>3</sup>NeRRe Therapeutics, Stevenage, United Kingdom; <sup>4</sup>Cytel, Waltham, MA; <sup>5</sup>Bayer CC AG, Basel, Switzerland; <sup>6</sup>Brigham and Women's Hospital, Harvard Medical School, Boston, MA; <sup>7</sup>Queen Charlotte's and Chelsea and Westminster Hospitals, Imperial College, London, United Kingdom; <sup>8</sup>Bayer AG, Berlin, Germany.

E.B. was employed at NeRRe Therapeutics, Stevenage, United Kingdom at the time the research was done.

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Address correspondence to: James A. Simon, MD, IntimMedicine Specialists, 1850 M St, NW, Suite 450, Washington, DC 20036. E-mail: [jsimon@intimmedicine.com](mailto:jsimon@intimmedicine.com)

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Vasomotor symptoms (VMS) and sleep disturbances are some of the most frequent and bothersome symptoms associated with menopause.<sup>1-4</sup> VMS are experienced by up to 80% of women during the menopausal transition, lasting on average 7 to 10 years after the last menstrual period,<sup>5-7</sup> with a third of women reporting very frequent or severe symptoms.<sup>8,9</sup> Around 40% to 60% of women experience sleep disturbances during the menopausal transition.

Hormone therapy is currently the most effective treatment option approved for the management of VMS.<sup>10</sup> However, many women are not candidates for hormone therapy because of medical contraindications or choose not to use it because of personal preferences.<sup>11-13</sup> There is therefore an unmet need for safe and effective nonhormone options to treat VMS associated with menopause.

Evolving evidence supports a central role of hypothalamic, estrogen-sensitive kisspeptin, neurokinin (NK)-B, and dynorphin (KNDy) neurons in thermoregulation and the etiology of VMS.<sup>14-19</sup> KNDy neurons express substance P and NK-B (NK-1 receptor [NK-1R] and NK-3R endogenous ligands, respectively), which may be involved in the modulation of VMS related to menopause.<sup>14,20-23</sup> Substance P and NK-1R may also modulate sleep effects related to menopause and contribute to peripheral vasodilatation.<sup>24-27</sup> Therefore, targeting NK-1R/substance P and NK-3R/NKB signaling may offer a nonhormone way to treat directly the cause of VMS and sleep disturbances associated with menopause.

Elinzanetant (NT-814) is a novel, selective NK-1,3R antagonist in development for the treatment of moderate-to-severe VMS associated with menopause. It is the first dual antagonist targeting both NK-1 and NK-3 receptors. NK-1R-specific antagonism has previously shown efficacy in primary insomnia and mood disorders not related to menopause.<sup>28-32</sup> However, the mechanism behind sleep disturbances associated with menopause is not fully understood, and there are no data on the impact of NK-1R antagonism on sleep disorders associated with menopause. Elinzanetant has previously been evaluated in a phase 2a randomized, placebo-controlled, multiple ascending dose trial (RELENT-1), where it demonstrated rapid and marked reductions in the frequency and severity of VMS.<sup>23</sup> The objectives of this phase 2b trial (SWITCH-1) were to assess further the efficacy and safety of elinzanetant in women experiencing bothersome VMS, evaluate dose-response, and, secondarily, to investigate the impact of elinzanetant on sleep disturbances and quality of life associated with menopause.

## METHODS

### Study design

SWITCH-1 was a multicenter, multicountry, double-blind, placebo-controlled, dose-range finding study with an adaptive randomization design evaluating elinzanetant in postmenopausal women aged 40 to 65 years. Menopause was defined as either (1) at least 12 months of spontaneous amenorrhea, (2) at least 6 months of spontaneous amenorrhea with serum follicle-stimulating hormone levels of more than 40 mIU/mL and serum estradiol less than 30 pg/mL, or (3) at least 6 weeks of postsurgical bilateral oophorectomy with or without hysterectomy. The study protocol and

statistical analysis plan are available in Supplemental Digital Content (Supplemental Data 1, <http://links.lww.com/MENO/B68>).

Institutional review board and ethics committee approval was obtained for all study sites, and all participants provided written informed consent. A 3-week initial screening period was used to assess eligibility. This 3-week period included a single-blind placebo run-in in the last 2 weeks in which participants received placebo once daily. To be eligible for the study, participants needed to meet the inclusion criteria (Supplemental Table 1, <http://links.lww.com/MENO/B69>), including recording on average at least seven moderate or severe VMS per day (see definition hereinafter) over the past 7 days of the screening period.

Eligible participants were initially randomized 1:1:1:1 and stratified by region (North America [United States and Canada] versus United Kingdom) to receive either once-daily elinzanetant (40, 80, 120, or 160 mg, soft gel capsules) or matching placebo for 12 weeks followed by a 4-week off-treatment follow-up (Supplemental Fig. 1, <http://links.lww.com/MENO/B69>). Participants were to take their assigned treatment orally at the same time each day.

The trial used an adaptive design algorithm based on Bayesian Emax dose-response modeling<sup>33</sup> and *T* statistic adaptive dose-finding design,<sup>34</sup> which provided dose assignment recommendations. An unblinded data review committee reviewed these recommendations, the model outputs for VMS frequency and severity, and emerging safety data and determined changes to the randomization ratio, if appropriate, to optimize sample size to improve the probability of finding effective doses.

### Data collection

Participants recorded the frequency and severity of VMS and the number of nighttime awakenings secondary to VMS twice daily in electronic diaries (eDiaries). Severity was scored on a scale of 0 to 3, with 0 representing none; 1, mild (sensation of heat without sweating); 2, moderate (sensation of heat with sweating but able to continue activity); and 3, severe (sensation of heat with sweating, causing cessation of activity). Any VMS causing a nighttime awakening by definition was considered severe.

The Insomnia Severity Index (ISI) questionnaire and Pittsburgh Sleep Quality Index (PSQI) were used to assess participants' sleep, whereas the Menopause-specific Quality-of-Life questionnaire intervention version (MenQoL-I) assessed quality of life (Supplemental Table 2, <http://links.lww.com/MENO/B69>). A decrease in score in each instrument corresponds to an improvement in symptoms. Participants completed the questionnaires during clinic visits at baseline and weeks 4, 8, 12, and 16.

Safety was assessed through adverse event monitoring. Other routine assessments included medical history, physical examinations, 12-lead electrocardiograms, suicide severity rating, clinical laboratory assessments, vital signs, and bone turnover markers. For changes in liver enzymes, only increases three or more times the upper limit of normal (ULN) were considered relevant, as per US Food and Drug Administration guidance.<sup>35</sup>

### Endpoints

The coprimary efficacy endpoints were mean change in the frequency and severity of moderate-to-severe VMS compared with placebo from baseline to weeks 4 and 12. Secondary endpoints

included the mean change from baseline compared with placebo of moderate-to-severe VMS frequency and severity at weeks 1, 2, 8, and 16; number of nighttime awakenings secondary to VMS at weeks 1, 2, 4, 8, 12, and 16; and ISI, PSQI, and MenQoL-I scores at weeks 4, 8, 12, and 16.

**Statistical analysis**

Assuming a common standard deviation of 4.4, n = 27 per treatment group would give approximately 95% power via trend test across all doses including placebo if the true underlying dose-response was nondecreasing from a reduction of four VMS on placebo up to eight on the highest dose of elinzanetant. Thus, the initial sample size was planned to be 33 participants per treatment group (165 in total) to allow for participants dropping out.

Descriptive statistical analyses were performed on all endpoint time points using Statistical Analysis System, version 9.4. Formal statistical hypothesis testing was performed at the two-sided, 0.05 level of significance for VMS frequency, severity, and nighttime awakenings secondary to VMS at all time points up to week 12 and ISI, PSQI, and MenQoL-I scores at weeks 4 and 12. Efficacy analyses were performed on the full analysis set, which included all randomized participants who received at least one dose of the study drug and had VMS data for at least 7 days of posttreatment assessments. Endpoints were analyzed using a mixed-effect model repeated measures approach incorporating postrandomization data up to week 12. Pairwise statistical comparisons were performed for each elinzanetant dose group versus placebo and least square (LS) means, SE, and 95% CI for the treatment difference were reported. Safety endpoints were summarized in all participants who received at least one dose of study drug.

**RESULTS**

SWITCH-1 was conducted at 25 sites across the United States, United Kingdom, and Canada. In total, 760 participants were screened, 199 were randomized, and 180 completed treatment (Fig. 1). Based on emerging efficacy data, the data review committee chose to discontinue randomization to the 80 mg and 40 mg

doses after 17 and 31 participants were enrolled in these groups, respectively. All randomized participants were included in both the full analysis set and safety analysis set. Baseline demographics, VMS, sleep, quality of life, and menopause characteristics were well balanced between treatment groups and indicated a high symptom burden (Table 1; Supplemental Tables 3 and 6-9, <http://links.lww.com/MENO/B69>).

**Vasomotor symptoms**

Compared with placebo, there were statistically significant and clinically relevant reductions (improvements) in the mean daily frequency of moderate-to-severe VMS with elinzanetant 120 mg at week 4 (difference in LS means [SE], -3.93 [1.02];  $P < 0.001$ ) and week 12 (-2.95 [1.15];  $P = 0.01$ ) (Fig. 2). The improvements with elinzanetant 160 mg were significant at week 4 (-2.63 [1.03];  $P = 0.01$ ) but not week 12 (-1.78 [1.19];  $P = 0.13$ ). Improvements with elinzanetant 40 mg and 80 mg were observed but not statistically significant compared with placebo at either of the primary endpoint time points.

Statistically significant improvements compared with placebo in the mean daily frequency of moderate-to-severe VMS were achieved by week 1 for both elinzanetant 120 mg (difference in LS means [SE], -1.80 [0.67];  $P = 0.008$ ) and 160 mg (-1.69 [0.67];  $P = 0.01$ ) (Fig. 2). Improvements tended to increase throughout treatment and returned toward baseline 4 weeks after treatment discontinuation (Supplemental Table 4, <http://links.lww.com/MENO/B69>).

Reductions in mean weekly severity of moderate-to-severe VMS followed a similar trend; however, reductions were only significant compared with placebo for elinzanetant 160 mg at week 12 (0.27 [0.13];  $P = 0.048$ ) (Fig. 2; Supplemental Table 5, <http://links.lww.com/MENO/B69>).

**Sleep and quality of life**

Reductions (improvements) in the frequency of nighttime awakenings secondary to VMS were significantly larger compared with placebo for elinzanetant 120 mg at weeks 1, 2, 4, and 8 ( $P = 0.006$  to  $P = 0.049$ ) but not at week 12 (Supplemental

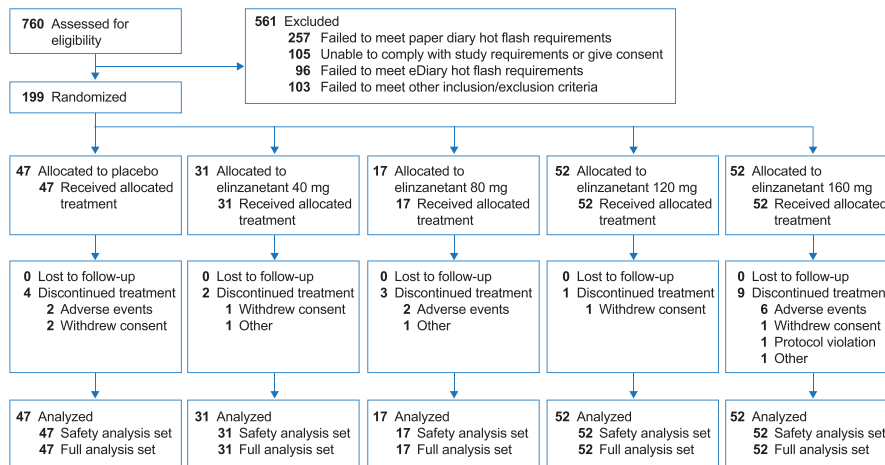


FIG. 1. Disposition of study participants.

TABLE 1. Baseline demographics and characteristics

Parameter/category	Placebo group (N = 47)	Elinzanetant group				Total elinzanetant (N = 152)
		40 mg (n = 31)	80 mg (n = 17)	120 mg (n = 52)	160 mg (n = 52)	
Demographics (safety analysis set)						
Age, mean (SD) (y)	55.6 (4.1)	55.4 (4.0)	55.9 (4.2)	54.8 (4.4)	55.0 (3.8)	55.1 (4.1)
Race, n (%)						
Asian	2 (4)	0	0	1 (2)	1 (2)	2 (1.3)
Black or African American	6 (13)	5 (16)	3 (18)	13 (25)	11 (21)	32 (21.1)
White	38 (81)	24 (77)	13 (77)	37 (71)	40 (77)	114 (75.0)
Other <sup>a</sup>	1 (2)	2 (7)	1 (6)	1 (2)	0	4 (2.6)
BMI, mean (SD) (kg/m <sup>2</sup> )	28.56 (3.83)	27.72 (4.88)	29.56 (5.02)	27.24 (4.64)	27.72 (4.87)	27.76 (4.81)
Moderate and severe VMS characteristics (full analysis set), mean (SD)						
Frequency, daily	11.82 (4.42)	12.13 (8.81)	14.55 (5.87)	13.54 (7.17)	12.92 (6.90)	13.16 (7.28)
Severity, weekly	2.54 (0.20)	2.51 (0.26)	2.63 (0.24)	2.54 (0.24)	2.54 (0.26)	2.55 (0.25)

BMI, body mass index; VMS, vasomotor symptoms.

<sup>a</sup>No additional detail was collected for participants in this category.

Table 6, <http://links.lww.com/MENO/B69>). Improvements were not significant compared with placebo for other doses.

Compared with placebo, there were statistically significant improvements in ISI score at weeks 4 and 12 for elinzanetant 120 mg (differences in LS means [SE],  $-3.41$  [0.92];  $P < 0.001$  and  $-4.27$  [1.01];  $P < 0.001$ , respectively) and 160 mg ( $-3.28$  [0.95];  $P < 0.001$  and  $-4.85$  [1.05];  $P < 0.001$ , respectively) (Fig. 3A). Clinically meaningful improvements of at least a 6-point reduction were achieved at weeks 8 and 12 for elinzanetant 120 mg and week 12 for elinzanetant 160 mg (Supplemental Table 7, <http://links.lww.com/MENO/B69>).<sup>36</sup> Improvements in ISI score were not significant compared with placebo for lower doses except for at week 12 for elinzanetant 80 mg ( $P = 0.008$ ).

Compared with placebo, there were statistically significant improvements in PSQI total score at weeks 4 and 12 for elinzanetant 120 mg (difference in LS means [SE],  $-2.05$  [0.51];  $P < 0.001$  and  $-2.46$  [0.67];  $P < 0.001$ , respectively) and 160 mg ( $-1.90$  [0.52];

$P < 0.001$  and  $-2.14$  [0.69];  $P = 0.002$ , respectively) (Fig. 3B; Supplemental Table 7, <http://links.lww.com/MENO/B69>). Improvements in PSQI score were not significant compared with placebo for lower doses at any time points.

Improvements in overall MenQoL-I score were statistically significant compared with placebo at weeks 4 and 12 for elinzanetant 120 mg (difference in LS means [SE],  $-0.87$  [0.20];  $P < 0.001$  and  $-0.80$  [0.22];  $P < 0.001$ , respectively) and 160 mg ( $-0.61$  [0.21];  $P = 0.004$  and  $-0.77$  [0.23];  $P < 0.001$ , respectively) (Fig. 3C). Clinically meaningful improvements of at least a 1-point reduction were seen for elinzanetant 120 mg and 160 mg at weeks 4, 8, 12 and 16 (Supplemental Table 9, <http://links.lww.com/MENO/B69>).<sup>37</sup> Significant improvements compared with placebo were not seen for lower doses.

Improvements in sleep and quality of life returned toward baseline 4 weeks after treatment discontinuation (Supplemental Tables 6-9, <http://links.lww.com/MENO/B69>).

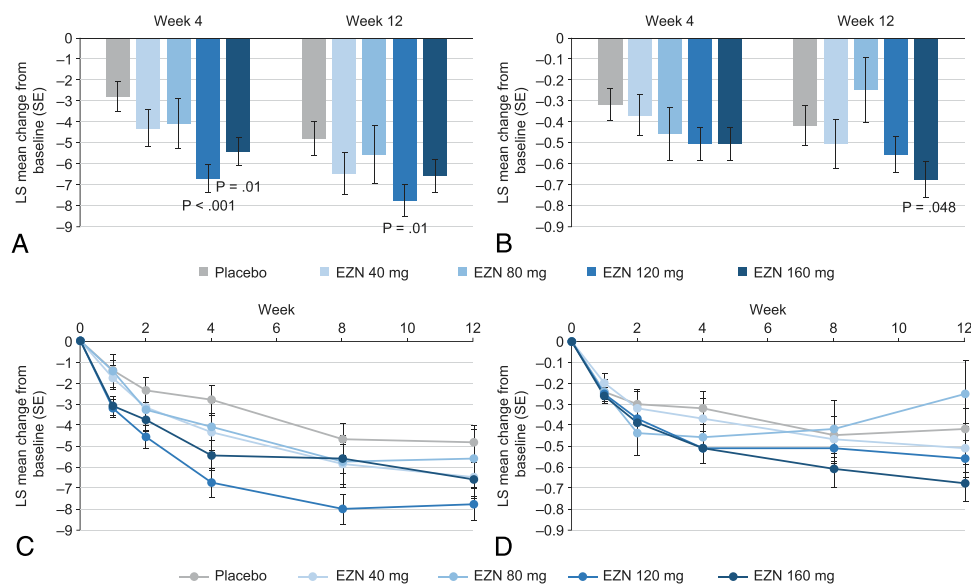
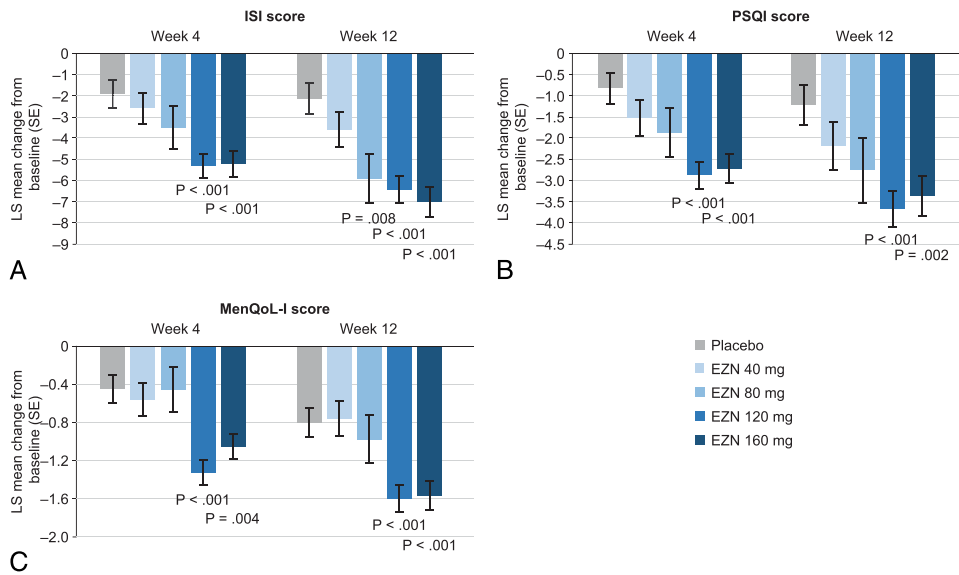


FIG. 2. Change from baseline in mean daily frequency (A, C) and weekly severity (B, D) of moderate and severe VMS by treatment group. EZN, elinzanetant; LS, least square; VMS, vasomotor symptoms.



**FIG. 3.** Change from baseline in ISI (A), PSQI (B), and MenQoL-I (C) score by treatment group at weeks 4 and 12. EZN, elinzanetant; ISI, Insomnia Severity Index questionnaire; LS, least square; MenQoL-I, Menopause-specific Quality-of-Life questionnaire intervention version; PSQI, Pittsburgh Sleep Quality Index.

**Safety**

Overall, 235 treatment-emergent adverse events (TEAEs) were reported in 67.8% (103 of 152) of participants in the elinzanetant groups, and 80 TEAEs were reported in 60% (28 of 47) of participants in the placebo group (Table 2). Most TEAEs were mild or moderate. The most frequently reported TEAEs across all treatment groups were headache, somnolence, and diarrhea. Seven of 152 elinzanetant-treated participants (4.6%) (2 of 17 [12%] for elinzanetant 40 mg and 5 of 52 [10%] for elinzanetant 160 mg) and 1 of 47 (2%) placebo-treated participants discontinued treatment because of adverse events; there were no discontinuations in the 120-mg dose group. Reasons for treatment discontinuation were prolonged QT and bradycardia; increased liver function test; headache; somnolence, abdominal distension, and dyspepsia; fatigue; depression and anxiety; and erythema multiforme in the elinzanetant groups and headache in the placebo group. The apparent prolonged QT leading to withdrawal of a participant was found to be erroneous (QTc was within normal

limits) on expert review. There was no obvious relationship between elinzanetant dose and the number of TEAEs. Somnolence was reported more frequently in the 160-mg dose and 40-mg dose groups compared with other doses, at a similar incidence in each group. Dizziness was only reported at higher doses of elinzanetant (120 and 160 mg); however, all incidences of dizziness were considered unrelated to treatment by the investigators.

There were sporadic increases in transaminases during treatment of no more than three times the ULN, but these were of equal frequency and magnitude in placebo- and elinzanetant-treated participants (11% and 8.8%, respectively) and were not considered clinically relevant. Two participants randomized to elinzanetant (both 80 mg) showed increases in transaminases three or more times the ULN; however, these participants had no detectable elinzanetant in plasma samples drawn at the same time as the enzyme increases and were considered to be noncompliant with study medication. In one of the two, there was also a marked increase in creatine kinase, suggesting that the transaminase increase

**TABLE 2.** Treatment-emergent adverse events by treatment group

AE category (preferred term) <sup>a</sup>	Placebo group, n (%) (N = 47)	Elinzanetant group, n (%)				Total (N = 152)
		40 mg (n = 31)	80 mg (n = 17)	120 mg (n = 52)	160 mg (n = 52)	
Any TEAEs	28 (60)	17 (55)	14 (82)	34 (65)	38 (73)	103 (67.8)
Serious TEAEs	2 (4)	0	1 (6)	1 (2)	1 (2)	3 (2)
TEAEs leading to discontinuation of study treatment	1 (2)	0	2 (12)	0	5 (10)	7 (4.6)
Most common TEAEs (occurring in ≥3 participants in any treatment group)						
Headache	6 (13)	3 (10)	2 (12)	6 (12)	4 (8)	15 (9.9)
Somnolence	1 (2)	3 (10)	1 (6)	2 (4)	6 (12)	12 (7.9)
Dizziness	0	0	0	3 (6)	3 (6)	6 (3.9)
Nasopharyngitis	4 (9)	1 (3)	0	3 (6)	0	4 (2.6)
Diarrhea	3 (6)	2 (6)	2 (12)	3 (6)	3 (6)	10 (6.6)
Blood creatine phosphatase increased	1 (2)	1 (3)	1 (6)	3 (6)	1 (2)	6 (3.9)
Fatigue	0	3 (10)	1 (6)	1 (2)	4 (8)	9 (5.9)

AE, adverse event; TEAEs, treatment-emergent adverse events.

<sup>a</sup>Coded using MedDRA version 21.1.

in this participant was likely to have been of muscle origin. There was no evidence of drug-related liver toxicity. No safety concerns were seen in any other routine safety assessments.

## DISCUSSION

SWITCH-1 is the first phase 2b study to demonstrate significant improvements in menopause-related symptoms, such as VMS and sleep disturbance, and improved quality of life with a selective NK-1,3R antagonist in postmenopausal women. Although improvements were observed in placebo-treated participants, consistent with other studies of VMS treatments,<sup>38-41</sup> greater improvements were seen across elinzanetant doses over the treatment period. In particular, improvements with elinzanetant 120 mg and 160 mg were statistically significant compared with placebo for VMS frequency (except for elinzanetant 160 mg at week 12), ISI score, PSQI score, and MenQoL-I score. Reductions in VMS frequency compared with placebo at the 120-mg dose were similar to those seen with hormone therapy and NK-3R antagonists and met the threshold for clinical relevance of a reduction of two or more per day beyond that achieved by placebo.<sup>38-42</sup>

The findings of this study further support the potential of NK signaling for the rapid treatment of VMS. Elinzanetant 120 mg and 160 mg led to meaningful reductions in VMS frequency after only 1 week of treatment. This is consistent with results from RELENT-1, in which similarly rapid reductions in VMS frequency were shown with a 150-mg dose of elinzanetant, and studies of NK-3R antagonists that demonstrate maximum efficacy within weeks.<sup>38,39,43</sup> The effect on VMS seen with elinzanetant may be mediated by suppression of KNDy neuron hyperactivation and an effect on peripheral vasodilatation through NK-1R antagonism in peripheral blood vessels.

In some of our analyses, elinzanetant 120 mg seems to have a greater benefit than elinzanetant 160 mg, particularly for VMS frequency. However, findings for elinzanetant 160 mg were skewed by a single participant in this group whose VMS frequency increased by more than 200% from baseline at times during the study. In a prespecified nonparametric analysis (data not shown) and an exploratory analysis excluding high outliers (ie, the one participant in the 160-mg group), reductions in mean VMS frequency were similar to that of the 120-mg dose and statistically significant compared with placebo.

Although VMS severity showed marked reductions across the higher elinzanetant doses, reductions were only significant compared with placebo at week 12 for elinzanetant 160 mg. Despite VMS severity being used to assess efficacy of VMS treatments by some regulatory authorities, it is recognized as a problematic endpoint because average severity takes no account of the number of VMS episodes overall.<sup>44</sup>

VMS that occur at night can be particularly distressing for women and disrupt sleep. This study did not require sleep disturbance for eligibility and participants recorded a low baseline number of nighttime awakenings. Reductions in nighttime awakenings secondary to VMS therefore were small and generally did not reach statistical significance. However, many women with little VMS interference report experiencing sleep disturbance during the menopause.<sup>45</sup> In this study, despite a low number of

self-reported awakenings due to VMS, at baseline, participants reported a high degree of sleep disturbance with average ISI scores indicative of moderate insomnia (8-14) and PSQI scores in the range associated with fatigue (>8).<sup>46</sup> After treatment with elinzanetant 120 mg and 160 mg, mean ISI scores fell to the subthreshold insomnia range (5-7) and PSQI scores fell below the level associated with fatigue. The present results support that antagonism of both NK-1R and NK-3R confers a benefit on sleep disturbance associated with menopause, and a reduction in sleep disturbance because of fewer awakenings secondary to VMS.

In a recent survey, sleep disturbances were rated as more bothersome than VMS as measured by the MenQoL questionnaire and had a greater impact on work productivity and day-to-day activities.<sup>1</sup> Treatment with elinzanetant 120 mg and 160 mg in this study resulted in statistically significant and clinically meaningful improvements in overall MenQoL-I scores, indicating improved menopause-specific quality of life.<sup>37</sup> These improvements in quality of life may have arisen because of participants experiencing fewer VMS and sleeping better or from the combination of these effects contributing to a greater sense of well-being, although it is not possible to determine the exact cause from our study.

Elinzanetant was well tolerated with no TEAEs of concern at any doses tested. There were no clear differences in the incidences of TEAEs between the treatment groups, although a slightly higher incidence of somnolence was reported for elinzanetant 160 mg (Table 2). Owing to previous reports of increases in liver enzymes with some single-mechanism NK-3R antagonists,<sup>38,39</sup> liver enzymes were monitored closely in SWITCH-1. There were significant transaminase increases in two elinzanetant-treated participants, but elinzanetant was undetectable in the plasma of these participants, suggesting that both were noncompliant with study medication.

The strengths of the study include its randomized, placebo-controlled adaptive design and the standardization of procedures across all study sites. The 2-week single-blind placebo run-in before the 12-week treatment period allowed 1 week for participants to familiarize themselves with the eDiaries and 1 week of baseline efficacy assessments. The inclusion of the placebo run-in, which has been used in similar studies previously, allowed for recording of baseline assessments under similar conditions to the treatment period and may provide the additional benefit of screening out participants with a high placebo response who would not have benefitted further from treatment.<sup>47</sup> eDiaries included time lock-outs to ensure that only contemporaneous data could be entered, improving the robustness of data. A key limitation is the high entry criteria for VMS frequency and severity; these criteria are used to support regulatory approval of VMS treatments but represent a barrier to study participation, resulting in many participants being ineligible at screening. Accordingly, the efficacy in patients with a lower VMS burden could not be investigated in this study. In addition, the use of an adaptive randomization schema aimed to improve the efficiency of the trial by reducing allocation to doses that appeared suboptimal. This resulted in smaller treatment groups for elinzanetant 40 mg and 80 mg, and consequently, the statistical analyses of these two doses have less power than the

two higher dose groups. However, the reduced power at lower doses was offset by increased power for the effective doses. Finally, there were no minimum eligibility criteria for nighttime awakenings secondary to VMS, and the average baseline frequency of these awakenings was low. Absolute reductions over the treatment period were small, and the study was not sufficiently powered to show statistical significance with these small differences.

## CONCLUSIONS

Taken together, findings from our study suggest that, relative to other elinzanetant doses tested, the 120-mg dose offers clinically important efficacy across a range of menopause-related symptoms with the most favorable benefit/risk profile. Elinzanetant demonstrated a generally dose-ordered response across all efficacy outcomes with no additional benefit observed with the 160-mg dose, suggesting a plateau of effect at 120 mg. The efficacy and safety of elinzanetant 120 mg will be further evaluated in a phase 3 program (NCT05042362, NCT05099159, NCT05030584).

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**Data sharing statement:** see Supplemental Digital Content, Supplemental Data 2, <http://links.lww.com/MENO/B70>.

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