ORIGINAL ARTICLE

Elinzanetant for Vasomotor Symptoms from Endocrine Therapy for Breast Cancer

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ABSTRACT

BACKGROUND

Women receiving endocrine therapy for hormone receptor (HR)–positive breast cancer or its prevention among those at high risk for breast cancer commonly have vasomotor symptoms. Data are lacking on the effects of elinzanetant, a neurokinin-targeted therapy shown to be effective in treating vasomotor symptoms, in this population.

METHODS

We performed a phase 3 trial involving women 18 to 70 years of age with moderate-to-severe vasomotor symptoms associated with endocrine therapy for HR-positive breast cancer or its prevention. Women were randomly assigned in a 2:1 ratio to receive once-daily elinzanetant at a dose of 120 mg for 52 weeks or once-daily placebo for 12 weeks followed by once-daily elinzanetant at a dose of 120 mg for 40 weeks. The primary end points were the change in the mean daily frequency of moderate-to-severe vasomotor symptoms from baseline to week 4 and to week 12.

RESULTS

A total of 316 participants were assigned to the elinzanetant group and 158 to the placebo–elinzanetant group. At baseline, the mean daily frequency of moderate-to-severe vasomotor symptoms was 11.4 episodes (95% confidence interval [CI], 10.7 to 12.2) in the elinzanetant group and 11.5 episodes (95% CI, 10.5 to 12.5) in the placebo–elinzanetant group. At week 4, the mean change from baseline in the mean daily frequency of moderate-to-severe vasomotor symptoms was −6.5 episodes (95% CI, −7.2 to −5.8) among those who were receiving elinzanetant and −3.0 episodes (95% CI, −3.9 to −2.2) among those who were receiving placebo (least-squares mean difference, −3.5 episodes; 95% CI, −4.4 to −2.6; P<0.001). At week 12, the mean change was −7.8 episodes (95% CI, −8.5 to −7.1) among those receiving elinzanetant and −4.2 episodes (95% CI, −5.2 to −3.2) among those receiving placebo (least-squares mean difference, −3.4 episodes; 95% CI, −4.2 to −2.5; P<0.001). During weeks 1 through 12, a total of 220 participants (69.8%) receiving elinzanetant and 98 (62.0%) receiving placebo reported at least one adverse event that occurred while receiving elinzanetant or placebo, with the most common being headache, fatigue, and somnolence. Serious adverse events occurred during weeks 1 through 12 in 8 participants (2.5%) receiving elinzanetant and 1 participant (0.6%) receiving placebo.

CONCLUSIONS

Elinzanetant led to a significantly lower frequency of vasomotor symptoms associated with endocrine therapy than placebo. (Funded by Bayer; OASIS-4 ClinicalTrials.gov number, NCT05587296.)

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CME

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Breast cancer accounts for 30% of all cancers in women, with hormone receptor (HR)–positive cancers comprising approximately 70% of all breast cancers.[1] Guidelines recommend that women with HR-positive breast cancer undergo treatment for at least 5 years (and for up to 10 years) with endocrine therapy (antiestrogen agents such as tamoxifen and aromatase inhibitors) with or without gonadotropin-releasing hormone (GnRH) analogues,[2-5] because this regimen has been shown to substantially reduce the rate of disease recurrence and mortality.[6,7]

Vasomotor symptoms (also known as hot flashes) are common adverse reactions to endocrine therapy.[8-12] Vasomotor symptoms associated with endocrine therapy can be more severe than those associated with natural menopause, particularly in younger women who often receive concomitant GnRH analogues.[13] Adverse reactions to endocrine therapy negatively affect health-related quality of life and can lead to nonadherence.[10,14-18]

Elinzanetant is a neurokinin (NK)-targeted therapy in development for the treatment of vasomotor symptoms associated with menopause that specifically antagonizes both NK-1 and NK-3 receptors. Increasing evidence indicates that hypothalamic kisspeptin–neurokinin–dynorphin (KNDy) neurons play a role in thermoregulation.[19] KNDy neurons express receptor–ligand systems, including NK-1 and NK-3 receptors and their respective ligands, substance P and neurokinin B. Declining estrogenic activity that results from natural menopause or endocrine therapy leads to hypertrophy and hyperactivity of KNDy neurons. The resulting hypertrophy and hyperactivity are accompanied by elevated expression of neurokinin B and substance P,[8,19-22] which disrupts thermoregulation and results in subsequent vasomotor symptoms.[8] NK-1 receptors may also have a role in peripheral vasodilatation and primary insomnia.[23,24]

In two pivotal phase 3, 26-week trials (OASIS-1 and OASIS-2) involving women with vasomotor symptoms associated with menopause, treatment with elinzanetant led to a significantly lower frequency and severity of moderate-to-severe vasomotor symptoms, a greater decrease in sleep disturbances, and greater improvements in menopause-related quality of life than placebo.[25] The OASIS-3 trial supported these results over a longer duration of up to 52 weeks.[26] The current trial, OASIS-4, assessed the efficacy and safety of elinzanetant at a dose of 120 mg for the treatment of vasomotor symptoms associated with endocrine therapy among women with or at high risk for HR-positive breast cancer.

METHODS

STUDY DESIGN

We conducted a 52-week, phase 3, interventional, double-blind, randomized, placebo-controlled trial at 90 sites in Europe, Canada, Israel, and Kazakhstan. Institutional review board and ethics committee approval was obtained from each trial site. The trial was conducted in accordance with the principles of the Declaration of Helsinki and the Council for International Organizations of Medical Sciences International Ethical Guidelines. All the participants provided written informed consent. A data and safety monitoring board reviewed the data collected in this trial. Participant engagement was sought during the protocol design and selection of end points.

Participants who completed 52 weeks of the trial regimen were offered the opportunity to continue treatment with elinzanetant for an additional 2 years. For those who consented, safety data are being collected during this extension period; these data are not included here.

The last author and two other authors employed by the sponsor vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol (available with the full text of this article at NEJM.org). Bayer (the sponsor) funded the trial and was involved in the trial design, the handling and analyses of the data, and the preparation of the submitted manuscript.

PARTICIPANTS

We enrolled women 18 to 70 years of age who were receiving endocrine therapy (tamoxifen or aromatase inhibitors with or without GnRH analogues) for HR-positive breast cancer or its prevention among those at high risk for breast cancer and had at least 35 moderate-to-severe vasomotor symptoms per week that were associated with endocrine therapy. The trial was designed to enroll at least 40% of participants receiving tamoxifen and at least 40% receiving aromatase inhibitors.

Exclusion criteria were an initial diagnosis of metastatic HR-positive breast cancer or a recurrence of HR-positive breast cancer while receiving endocrine therapy; surgical or nonsurgical treat-

ment for breast cancer (with the exception of tamoxifen, aromatase inhibitors, and GnRH analogues) within 3 months before signing informed consent; surgery, chemotherapy, radiotherapy, or immunotherapy that was scheduled to take place during the trial; or concomitant administration of certain medications (see the Randomization and Intervention section below). Details of inclusion and exclusion criteria are provided in Table S1 in the Supplementary Appendix (available at NEJM.org).

RANDOMIZATION AND INTERVENTION

Participants underwent a prescreening period of washout of prohibited concomitant medications, including hormonal, nonhormonal, antidepressant, and over-the-counter therapies that may influence vasomotor symptoms (excluding endocrine therapy) or the pharmacokinetics of elinzanetant, followed by screening to determine eligibility. Participants documented their intake of trial medication (including endocrine therapy) daily throughout the trial. Intake of prohibited medications during the trial was considered an important intercurrent event and was accounted for in the analysis (see the Supplementary Appendix).

Randomization was performed centrally with the use of an interactive voice and Web response system (IxRS). Eligible participants were randomly assigned in a 2:1 ratio to receive 120 mg of elinzanetant once daily for 52 weeks or identical-appearing placebo once daily for 12 weeks followed by 120 mg of elinzanetant once daily for 40 weeks. After treatment concluded, participants were followed for an additional 4 weeks (Fig. S1). All participant-reported outcomes used to assess efficacy were recorded on a handheld electronic device.

The investigators and participants were unaware of group assignments throughout the trial up to week 52. The sponsor was unaware of group assignments up to week 26, when the preplanned final efficacy analysis was performed.

EFFICACY END POINTS

The primary end points were the change in the mean daily frequency of moderate-to-severe vasomotor symptoms from baseline to week 4 and to week 12. The frequency of vasomotor symptoms was measured with the use of a hot-flash daily diary similar to diaries used in other clinical trials involving participants with vasomotor symptoms.[25] Participants recorded the number of mild (sensation of heat without sweating), moderate (sensation of heat with sweating), and severe (sensation of heat with sweating and causing cessation of activity) hot flashes they had during the night (morning diary) and day (evening diary). Participants were required to complete at least 11 days of diary entries during the 2 weeks before baseline to be eligible for trial enrollment.

Key secondary end points were the mean change from baseline to week 12 in the Patient-Reported Outcomes Measurement Information System Sleep Disturbance Short Form (PROMIS SD SF) 8b total T score (scores range from 28.9 to 76.5, with higher scores indicating more severe sleep disturbances) and the Menopause-Specific Quality of Life (MENQOL) questionnaire total score (scores range from 1 to 8, with higher scores indicating more impaired quality of life with respect to menopause symptoms).[25] Further details of the application and scoring of these questionnaires are provided in the Supplementary Methods section in the Supplementary Appendix.

Additional secondary end points were the change in the mean daily severity of moderate-to-severe vasomotor symptoms from baseline to weeks 4 and 12 and the change in the mean daily frequency of moderate-to-severe vasomotor symptoms from baseline to week 1 and over time. The severity of vasomotor symptoms was assessed with the hot-flash daily diary and a specific formula to calculate a numeric value (see Supplementary Methods). Exploratory end points included the percentage of participants who had a treatment response at weeks 4 and 12, which was defined as a reduction of at least 50% in the frequency of daily vasomotor symptoms. Further details are provided in the Supplementary Methods.

SAFETY

Adverse events were reported by the participants throughout the trial and were coded according to the *Medical Dictionary for Regulatory Activities*, version 27.1. Cervical smears, endometrial biopsies, transvaginal ultrasonography, and mammography were performed as a part of safety monitoring during screening and at the end of treatment, if applicable (details are provided in the Supplementary Methods). Other safety assessments included weight, vital signs, and laboratory assessments. A blinded independent external liver safety monitoring board assessed cases that met prespecified

criteria for close liver observation to identify potential drug-induced liver injury. An independent data and safety monitoring board monitored general safety. Additional details are provided in the Supplementary Methods.

PHARMACOKINETICS

Blood samples were collected at baseline; at trial weeks 1, 4, 8, 12, and 26; and at the end of treatment. The potential influence of endocrine therapy on the pharmacokinetics of elinzanetant and the influence of elinzanetant on the pharmacokinetics of tamoxifen (and its metabolites) and aromatase inhibitors (specifically anastrozole) was assessed (see the Supplementary Methods).

STATISTICAL ANALYSIS

Using a one-sided two-sample t-test (equal variance) and assuming independence between end points, an approximate normal distribution, and a 10% dropout rate at 3 months, we calculated that a sample of 405 participants (270 in the elinzanetant group and 135 in the placebo–elinzanetant group) would need to undergo randomization to have 365 participants with evaluable data (243 and 122 in the elinzanetant group and placebo–elinzanetant group, respectively) for the primary efficacy analysis. Assuming between-group differences in the mean (±SD) change in frequency of moderate-to-severe vasomotor symptoms from baseline to week 4 and week 12 of −2±3.6 and −2±4.3 episodes per day, respectively, and a between-group difference in the mean change in the PROMIS SD SF 8b total T score and the MENQOL total score from baseline to week 12 of −0.4±1.0 (for both), we estimated that an evaluable sample of 365 participants would provide approximately 90% power to detect a sig-

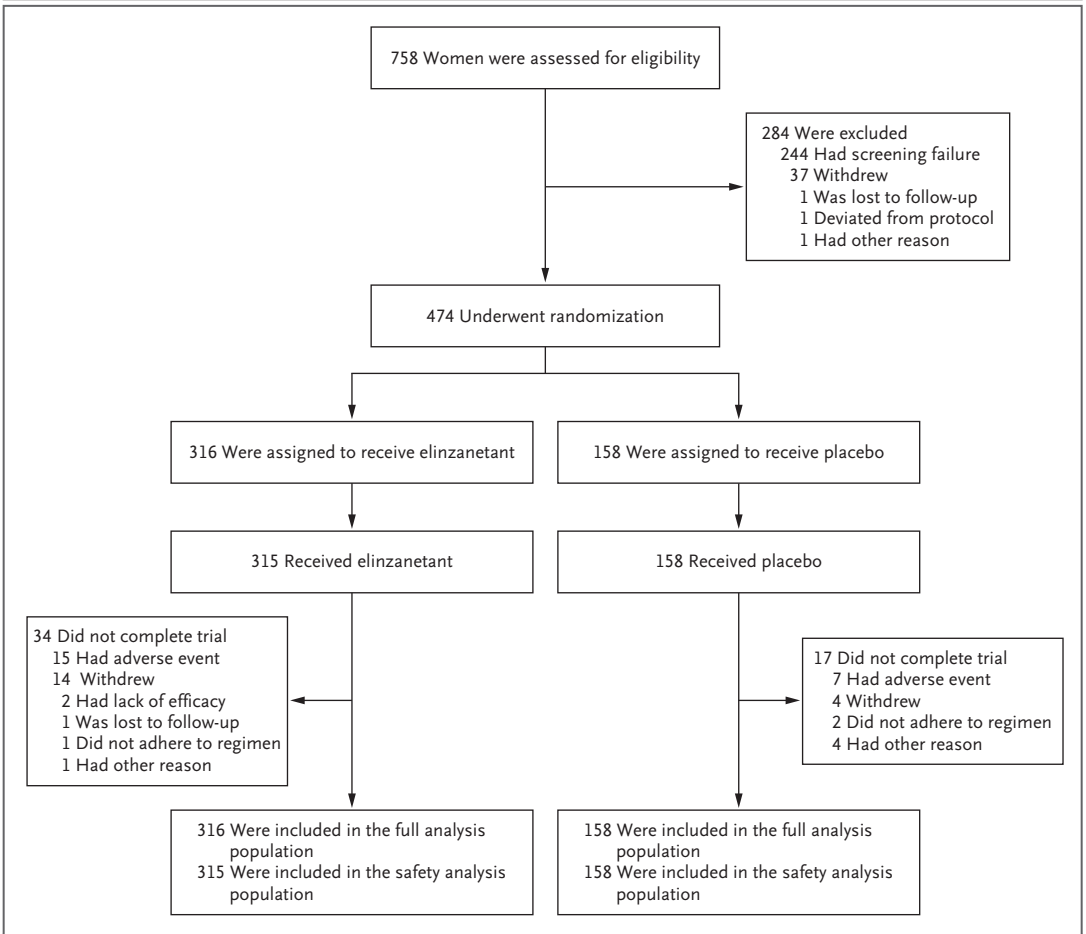

Figure 1. Screening and Randomization.

nificant between-group difference in the primary and key secondary end-point analyses (Table S2). In addition, we assumed a yearly dropout rate of 30% in both groups, which would result in approximately 189 participants in the elinzanetant group and 94 participants in the placebo–elinzanetant group at the 12-month follow-up. Randomization was stratified according to the type of endocrine therapy participants were receiving at baseline (tamoxifen vs. aromatase inhibitor).

Efficacy analyses were based on the full analysis population (all the participants who underwent

Table 1. Demographic and Clinical Characteristics of Participants at Baseline (Full Analysis Population).*

Characteristic	Elinzanetant (N=316)	Placebo (N=158)
Race or ethnic group — no. (%)†		
White	278 (88.0)	140 (88.6)
Black	6 (1.9)	1 (0.6)
Asian	1 (0.3)	1 (0.6)
American Indian or Alaska Native	2 (0.6)	1 (0.6)
Hispanic or Latino	7 (2.2)	5 (3.2)
Not reported	29 (9.2)	15 (9.5)
Age — yr	50.8±7.5	51.5±6.7
Body-mass index‡	26.1±4.6	26.8±4.7
Smoking history — no. (%)		
Never	201 (63.6)	108 (68.4)
Former	71 (22.5)	33 (20.9)
Current	44 (13.9)	17 (10.8)
Cancer status — no. (%)		
Current breast cancer	315 (99.7)	158 (100.0)
High risk for breast cancer	1 (0.3)	0
Stage at initial diagnosis — no. (%)		
Stage 0	8 (2.5)	8 (5.1)
Stage I	159 (50.3)	71 (44.9)
Stage II	127 (40.2)	67 (42.4)
Stage III	21 (6.6)	12 (7.6)
Not applicable§	1 (0.3)	0
Histologic findings — no. (%)		
Infiltrating ductal carcinoma not otherwise specified	219 (69.3)	97 (61.4)
Lobular carcinoma not otherwise specified	37 (11.7)	25 (15.8)
Ductal carcinoma in situ, solid type	19 (6.0)	9 (5.7)
Other	41 (13.0)	27 (17.1)
Type of endocrine treatment — no. (%)		
Tamoxifen	175 (55.4)	90 (57.0)
Aromatase inhibitors	141 (44.6)	68 (43.0)
Median duration of endocrine therapy (range) — mo	20.4 (0.0–97.2)	18.0 (1.2–116.4)

* Plus–minus values are means ±SD. The full analysis population included all participants who underwent randomization.
† Race and ethnic group were reported by the participants.
‡ The body-mass-index is the weight in kilograms divided by the square of the height in meters.
§ One participant in the elinzanetant group had no information on breast cancer status at diagnosis and was taking endocrine therapy for the prevention of breast cancer.

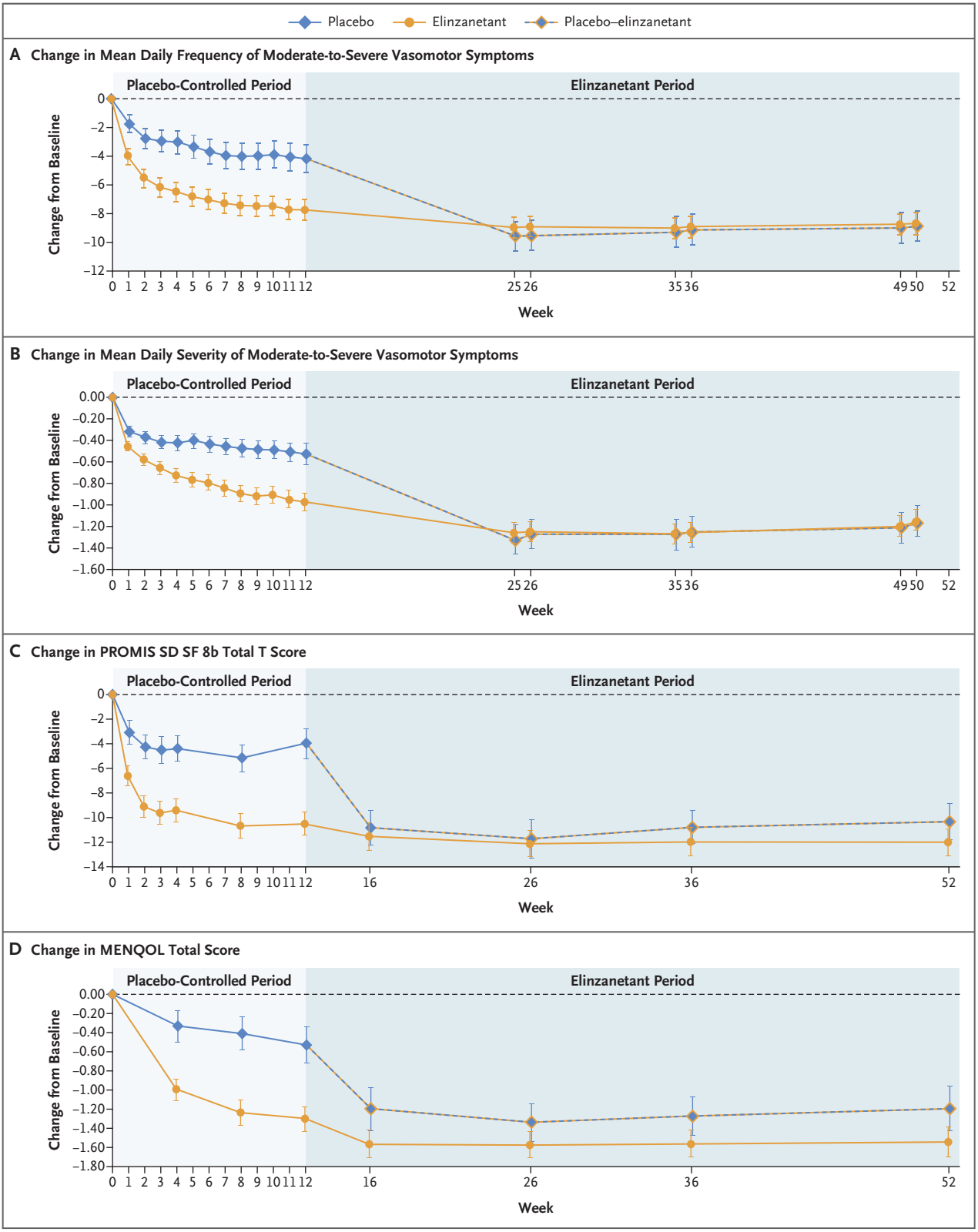

Figure 2 (facing page). Change over Time in Frequency and Severity of Vasomotor Symptoms and Patient-Reported Outcome Measures.

Shown is the mean change from baseline in the mean daily frequency of moderate-to-severe vasomotor symptoms (Panel A), the mean daily severity of vasomotor symptoms (Panel B), Patient-Reported Outcomes Measurement Information System Sleep Disturbance Short Form (PROMIS SD SF) 8b total T score (scores range from 28.9 to 76.5, with higher scores indicating more severe sleep disturbances) (Panel C), and the Menopause-Specific Quality of Life (MENQOL) questionnaire score (scores range from 1 to 8, with higher scores indicating more impaired menopause-related quality of life) (Panel D) in the full analysis population (all participants who underwent randomization). The mean daily severity of vasomotor symptoms was calculated by multiplying the number of mild episodes a participant had in a day by 1, the number of moderate episodes by 2, the number of severe episodes by 3, and then dividing the sum of these values by the total number of episodes the participant had that day. The mean daily value was set to 0 if the participant had no episodes that day. Additional details are provided in the Supplementary Methods. A decrease in the PROMIS SD SF 8b total T score and in the MENQOL total score indicates a decrease in sleep disturbances and an improvement in menopause-related quality of life, respectively. Participants in the placebo–elinzanetant group received placebo for 12 weeks followed by elinzanetant for 40 weeks. Confidence intervals have not been adjusted for multiplicity and should not be used to infer definitive treatment effects.

randomization), and safety analyses were based on all the participants who underwent randomization and received at least one dose of elinzanetant or placebo. Statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

The primary and key secondary efficacy end points were analyzed with the use of a mixed model with repeated measures with respect to the change from baseline values. A hierarchical testing strategy was applied to control the type I error at a two-sided alpha level of 0.05 when testing the primary and key secondary end points. The additional secondary end points and exploratory end points were not part of the hierarchical testing plan. Results are presented with 95% confidence intervals; the widths of the intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing. If data were not available for the diary-derived end points for more than 2 days within a week, the value for that week was set to "missing." Further details are provided in the Supplementary Methods. Other secondary and exploratory end points were assessed descriptively.

RESULTS

PARTICIPANTS

The trial was conducted between October 14, 2022, and November 14, 2024. Of the 758 participants who were screened, 474 underwent randomization, 444 completed 12 weeks of treatment, and 395 completed 52 weeks of treatment (Fig. 1). Only one participant was receiving endocrine therapy for the prevention of breast cancer. One participant in the elinzanetant group chose not to receive the trial intervention and was excluded from the safety analysis. Demographic characteristics were well balanced between the trial groups (Table 1). Breast cancer characteristics are provided in Table S3. The representativeness of the trial participants is summarized in Table S4. Adherence of the participants to their previously prescribed endocrine therapy remained stable from baseline throughout the trial. Of the participants who completed 52 weeks of treatment, 91.6% chose to enter the 2-year extension phase and continued receiving elinzanetant.

PRIMARY END POINTS

At baseline, the mean daily frequency of moderate-to-severe vasomotor symptoms was 11.4 episodes (95% confidence interval [CI], 10.7 to 12.2) in the elinzanetant group and 11.5 episodes (95% CI, 10.5 to 12.5) in the placebo–elinzanetant group. At week 4, the mean change from baseline in the daily frequency of moderate-to-severe vasomotor symptoms was −6.5 episodes (95% CI, −7.2 to −5.8) among participants who were receiving elinzanetant and −3.0 episodes (95% CI, −3.9 to −2.2) among those who were receiving placebo; the least-squares mean difference between the trial groups was −3.5 episodes (95% CI, −4.4 to −2.6; P<0.001) (Fig. 2A and Table S5). At week 12, the mean change from baseline was −7.8 episodes (95% CI, −8.5 to −7.1) and −4.2 episodes (95% CI, −5.2 to −3.2) in the two groups, respectively; the least-squares mean difference between the trial groups was −3.4 episodes (95% CI, −4.2 to −2.5; P<0.001).

KEY SECONDARY END POINTS

At baseline, the mean PROMIS SD SF 8b total T score was 60.6 (95% CI, 59.9 to 61.3) in the elinzanetant group and 60.7 (95% CI, 59.7 to 61.8) in the placebo–elinzanetant group, which indicated moderate sleep disturbance. The mean change in the PROMIS SD SF 8b total T score from baseline to week 12 was −10.6 points (95% CI, −11.5 to −9.6) among the participants who were receiving elinzanetant and −4.1 points (95% CI, −5.3 to −2.9) among those who were receiving placebo (least-squares mean difference between the trial groups, −6.1 points; 95% CI, −7.5 to −4.8; P<0.001) (Fig. 2C and Table S6).

The mean MENQOL total score at baseline was 4.8 (95% CI, 4.7 to 5.0) in the elinzanetant group and 4.8 (95% CI, 4.6, 5.0) in the placebo–elinzanetant group. The mean change in the MENQOL total score from baseline to week 12 was −1.3 points (95% CI, −1.4 to −1.2) among the participants receiving elinzanetant and −0.5 points (95% CI, −0.7 to −0.3) among those receiving placebo (least-squares mean difference between the trial groups, −0.7 points; 95% CI, −0.9 to −0.5; P<0.001) (Fig. 2D and Table S7).

OTHER SECONDARY AND EXPLORATORY END POINTS

The mean change from baseline to week 1 in the daily frequency of moderate-to-severe vasomotor symptoms was −4.0 episodes (95% CI, −4.6 to −3.5) among the participants receiving elinzanetant and −1.8 episodes (95% CI, −2.4 to −1.2) among those receiving placebo. Changes in the severity of vasomotor symptoms in the two groups are shown in Figure 2B and Table S8. In an exploratory analysis, 61.1% of the participants receiving elinzanetant (95% CI, 55.7 to 66.6) and 27.0% of those receiving placebo (95% CI, 19.9 to 34.0) had a treatment response at week 4 (a reduction of at least 50% in the frequency of daily moderate-to-severe vasomotor symptoms); the respective percentages at week 12 were 74.3% (95% CI, 69.3 to 79.3) and 35.8% (95% CI, 28.1 to 43.5).

SAFETY

During weeks 1 through 12, a total of 220 participants (69.8%) who were receiving elinzanetant and 98 (62.0%) who were receiving placebo had at least one adverse event that occurred while receiving the assigned active drug or placebo. Most of these adverse events were mild or moderate, with severe adverse events occurring in 13 participants (4.1%) receiving elinzanetant and 4 (2.5%) receiving placebo. Serious adverse events occurred during weeks 1 through 12 in 8 participants (2.5%) receiving elinzanetant and 1 participant (0.6%) receiving placebo. Somnolence, fatigue, and diarrhea were reported more frequently with elinzanetant than with placebo during weeks 1 through 12. No deaths occurred during the trial. Details of adverse events that occurred during weeks 1 through 12 and during weeks 13 through 52 of treatment are shown in Table 2 and Tables S9 and S10.

During weeks 13 through 52, one woman reported a new breast cancer, one woman reported recurrent breast cancer, and one woman reported progression of breast cancer to stage IV. In addition, one woman had suspected liver metastasis, and another had metastases to bone and the liver.

Elevations in liver-enzyme levels that fulfilled the prespecified criteria for close liver observation were observed in five women, and all of these elevations occurred while the women were taking elinzanetant. A cause other than the trial medication was documented for all cases (Tables S11 to S14). One case was considered serious because of high aminotransferase levels. The liver safety monitoring board concluded that all cases were reversible, with no case meeting the criteria for Hy's law, and that there did not appear to be a substantive hepatotoxicity signal with elinzanetant.

Endometrial biopsies were performed on the basis of findings (e.g., unexplained vaginal bleeding) in 33 women in the elinzanetant group and 14 in the placebo–elinzanetant group; 74.5% of these participants were receiving tamoxifen. All the participants with an evaluable sample in both trial groups had a benign finding as assessed by three independent trial pathologists. Two participants were reported to have endometrial hyperplasia: one participant received a diagnosis from a local pathologist, and one participant who declined to undergo an endometrial biopsy despite an endometrial thickness of more than 10 mm underwent ablation.

PHARMACOKINETICS

Endocrine therapy did not appear to have an effect on the pharmacokinetics of elinzanetant. No clinically relevant changes from baseline in the pharmacokinetics of tamoxifen (and its metabolites)

Table 2. Summary of Adverse Events That Occurred during the 52-Week Treatment Period (Safety Analysis Population).*

Adverse Event	Weeks 1–12		Weeks 13–26		Weeks 27–52
	Elinzanetant (N=315)	Placebo (N=158)	Elinzanetant (N=294)	Placebo–Elinzanetant (N=150)†	Elinzanetant (N=409)
	number of participants (percent)				
At least one	220 (69.8)	98 (62.0)	154 (52.4)	81 (54.0)	217 (53.1)
At least one severe	13 (4.1)	4 (2.5)	7 (2.4)	7 (4.7)	16 (3.9)
At least one that led to discontinuation of trial drug	23 (7.3)	4 (2.5)	4 (1.4)	6 (4.0)	3 (0.7)
At least one serious	8 (2.5)	1 (0.6)	8 (2.7)	4 (2.7)	18 (4.4)
Occurred in at least 5% of participants in any trial group					
Headache	30 (9.5)	20 (12.7)	13 (4.4)	7 (4.7)	11 (2.7)
Arthralgia	20 (6.3)	10 (6.3)	19 (6.5)	6 (4.0)	15 (3.7)
Fatigue	30 (9.5)	8 (5.1)	7 (2.4)	5 (3.3)	3 (0.7)
Somnolence	34 (10.8)	6 (3.8)	4 (1.4)	5 (3.3)	1 (0.2)
Diarrhea	16 (5.1)	3 (1.9)	6 (2.0)	4 (2.7)	7 (1.7)
Nausea	19 (6.0)	10 (6.3)	6 (2.0)	5 (3.3)	3 (0.7)

* The safety analysis population included all participants who underwent randomization and received at least one dose of elinzanetant or placebo.

† Participants in the placebo–elinzanetant group received placebo for 12 weeks followed by elinzanetant for 40 weeks. Results for this group for weeks 13 to 26 are reported separately from the elinzanetant group to allow evaluation of adverse events after the switch, when the patients in this group were receiving elinzanetant for the first time.

or anastrozole were observed in the elinzanetant group.

DISCUSSION

In this phase 3, multicenter, placebo-controlled trial involving women taking endocrine therapy for HR-positive breast cancer, elinzanetant led to a significantly lower daily frequency of moderate-to-severe vasomotor symptoms, a greater decrease in sleep disturbances, and a greater increase in menopause-related quality of life than placebo. These results are consistent with the previously published phase 3 trials involving women with vasomotor symptoms caused by natural or surgically induced menopause,[25,26] which shows the reproducibility of findings across populations.

Although there is currently no defined threshold for a clinically meaningful reduction in the frequency of moderate-to-severe vasomotor symptoms among women with vasomotor symptoms associated with endocrine therapy, a reduction from baseline of at least 50% is considered to be clinically meaningful on an individual level in the natural-menopause population.[27] In exploratory analyses, more than 70% of the participants treated with elinzanetant had a reduction in symptoms of at least 50% at 12 weeks, which is consistent with the results of the OASIS-1 and OASIS-2 trials.[25]

Vasomotor symptoms and sleep disturbances are among the most frequent and disruptive adverse symptoms associated with endocrine therapy.[28] These symptoms affect quality of life and potentially lower long-term adherence to therapy, which results in poorer breast cancer outcomes.[17,19,29,30] Reducing side effects while improving quality of life and long-term adherence are therefore key focuses of medical and patient communities.[31] Because women receiving endocrine therapy are not eligible to receive hormone therapy for menopause symptoms, management options include complementary medicines or lifestyle interventions, which have limited evidence of efficacy[32-34]; cognitive behavioral therapy, which can be challenging to access[35]; or other medications. Various selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibi-

tors, and other agents, such as gabapentin, are used off-label, but the benefits appear to be modest and inconsistent, and adverse effects are common.[36,37] The only nonhormonal drugs currently approved by the Food and Drug Administration for treatment of vasomotor symptoms include paroxetine and fezolinetant, with the latter being another neurokinin-targeted therapy. However, the use of paroxetine with tamoxifen is not recommended,[12] and published data on fezolinetant treatment specifically in women with breast cancer are not available; the use of either agent in this population is currently off-label.

Elinzanetant had a safety profile that was similar to that of placebo during 12 weeks and with extended use up to 52 weeks. On the basis of the available 52-week data for all the participants in both groups who received elinzanetant, the liver safety monitoring board concluded that there was no substantive hepatotoxicity signal with elinzanetant, a finding consistent with data from the OASIS-1, OASIS-2, and OASIS-3 trials.[25,26] Further data from the extension phase and real-world application will be helpful. Although we did not collect data on treatment satisfaction in this trial, the observation that 91.6% of the participants who completed 52 weeks of treatment chose to continue receiving elinzanetant through an optional 2-year extension suggests a high level of satisfaction.

This trial had limitations. Demographic characteristics were consistent with the populations of the European regions in which the majority of the trial sites were located, and most of the participants were White, which limits the generalizability of these findings to other populations. In addition, because only one participant was taking endocrine therapy for the prevention of breast cancer, conclusions regarding the efficacy of elinzanetant in this population cannot be drawn. Furthermore, although the patient-reported outcomes used in this trial are suitable for measuring the end points of interest, they are subjective. Longer-term assessment of adherence to endocrine therapy among women taking elinzanetant is warranted. Finally, recurrence of breast cancer and survival were not prespecified outcomes in this trial; future studies assessing these outcomes will be important.

In a finding consistent with the results of previous trials involving postmenopausal women, treatment with elinzanetant resulted in significant decreases in the frequency of vasomotor symptoms and in sleep disturbances and improvements in health-related quality of life among women with moderate-to-severe vasomotor symptoms taking endocrine therapy for breast cancer.

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