Menopause: The Journal of The Menopause Society
Vol. 00, No. 00, pp. 00-00
DOI: 10.1097/GME.0000000000002354

OPEN

ORIGINAL STUDY

Treating moderate-to-severe menopausal vasomotor symptoms with fezolinetant: analysis of responders using pooled data from two phase 3 studies (SKYLIGHT 1 and 2)

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Abstract

Objectives: The aims of the study were to further characterize the efficacy of fezolinetant for the treatment of moderate-to-severe vasomotor symptoms (VMS) due to menopause using responder analysis and to investigate whether efficacy, not adjusted for placebo, resulted in clinically meaningful within-patient change.

Methods: This prespecified analysis used pooled data from two phase 3, randomized, double-blind, placebo-controlled studies (SKYLIGHT 1 and 2). Responders were those experiencing ≥50%, ≥75%, ≥90%, or 100% reduction in VMS frequency from baseline to weeks 4 and 12. Responder analysis was performed for patient-reported outcome (PRO) measures to evaluate participants achieving a clinically meaningful within-patient change (not placebo adjusted) at week 4 and 12 versus baseline. Single responders were based on outcomes of VMS frequency, Patient-Reported Outcomes Measurement Information System Sleep Disturbance–Short Form 8b Total Score, Menopause-Specific Quality of Life (MENQoL) Total Score, and MENQoL VMS Domain Score. Double and triple responder analyses combined VMS frequency plus one or more of the PRO. Patient Global Impression of Change VMS was deemed a suitable anchor measure for meaningful within-patient change in VMS frequency.

Results: A greater proportion of fezolinetant-treated versus placebo-treated participants had ≥50%, ≥75%, ≥90%, or 100% reduction in VMS frequency from baseline to weeks 4 and 12. A greater proportion of responders were observed in the fezolinetant groups versus placebo at week 12 in all four single responder analyses. In the double and triple responder analyses, odds ratios were supportive of a beneficial effect for both doses of fezolinetant versus placebo.

Conclusions: Fezolinetant was associated with significantly higher within-patient clinically meaningful improvement in important PRO, including VMS frequency, PROMIS SD SF 8b Total Score, MENQoL Total Score, and MENQoL VMS Domain Score.

Key Words: Clinically meaningful – Efficacy – Fezolinetant – Responder – Vasomotor symptoms.

Received September 27, 2023; revised and accepted January 17, 2024.

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Data presentation: Data from this study were presented at the World Congress on Menopause; Lisbon, Portugal; October 26-29, 2022.

This study was sponsored by Astellas Pharma, Inc. Medical writing and editorial support were provided by Sue Cooper, CMPP, from Envision Pharma, Inc, and funded by the study sponsor.

Financial disclosure/conflicts of interest: R.E.N. reports past financial relationships (lecturer, member of advisory boards and/or consultant) with Boehringer Ingelheim, Eli Lilly, Endoceutics, Exeltis, Novo Nordisk, Palatin Technologies, Pfizer, Procter & Gamble, Teva Women's Health and Zambon; ongoing relationships with Abbott, Astellas, Bayer HealthCare, Fidia, Gedeon Richter, HRA Pharma, Merck & Co, Organon, Shionogi, Theramex and Viatris; serving as President elect of the International Menopause Society; and is a member of the Fezolinetant Scientific Steering Committee. K.A.J. reports being a study investigator and consultant for Astellas and a study investigator for iResearch Atlanta. P.S. reports being a consultant for Astellas; a board member for DMG and EMAS; President of the SGEM; speaker's fees for Theramex, Exeltis, Gedeon Richter, Besins Healthcare, and Jenapharm; and a member of the Fezolinetant Scientific Steering Committee. M.B., M.E., L.S. and F.D.O. are employees of Astellas Pharma Inc. A.M. and E.S. are employees of Astellas Pharma Europe Ltd.

Data sharing statement: Researchers may request access to anonymized participant-level data, trial-level data, and protocols from Astellas sponsored clinical trials at www.clinicalstudydatarequest.com. For the Astellas criteria on data sharing, see https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx.

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Vasomotor symptoms (VMS), characterized by hot flashes and/or night sweats and caused by disproportionate neuronal activity in the hypothalamic thermoregulatory center, can affect up to 80% of women during menopausal transition.[1,2] Vasomotor symptoms are moderate to severe for up to 50% of women, have a mean duration of 4.6 years after the final menstrual period,[3] and may persist/be observed for more than a decade after the menopause transition.[3,4]

Vasomotor symptoms are bothersome and can adversely affect health-related quality of life (HRQoL), including impact on sleep, concentration, mood, energy, sexual activity, and work/leisure activities.[5,6] In addition, frequent and persistent VMS are associated with adverse physiological health outcomes, including cardiovascular disease and lower bone density.[7-10]

Fezolinetant is a nonhormone, selective neurokinin 3 receptor (NK3R) antagonist that moderates neuronal activity in the thermoregulatory center in the hypothalamus. It has been approved at a once-daily dose of 45 mg by the US Food and Drug Administration for the treatment of moderate-to-severe VMS due to menopause and by the European Medicines Agency and the Australian Therapeutic Goods Administration for treatment of VMS associated with menopause.[11,12] The thermoregulatory center is innervated by kisspeptin/neurokinin B/dynorphin (KNDy) neurons, which are stimulated by the neuropeptide neurokinin B, acting at the NK3R and inhibited by estrogen. With declining estrogen levels in menopause, NK3R-mediated activation is unopposed, leading to hypertrophy of KNDy neurons and altered activity on the thermoregulatory center. Heat dissipation effectors are triggered by the thermoregulatory center.[13-15] Vasodilation in the skin causes heat loss, which can be experienced as hot flashes, sweating, and chills.[13-15] Fezolinetant blocks neurokinin B binding on the KNDy neuron, restoring normal sensitivity of the thermoregulatory center, thereby reducing the frequency and severity of moderate-to-severe VMS associated with menopause.[16-18]

Two phase 3 trials of fezolinetant, SKYLIGHT 1 (NCT04003155) and SKYLIGHT 2 (NCT04003142), have demonstrated that fezolinetant is efficacious for the treatment of moderate-to-severe VMS associated with menopause and is generally well tolerated.[19,20] At 12 weeks, least squares mean difference in VMS frequency versus placebo was −2.51 (95% confidence interval [CI], −3.20 to −1.82) for fezolinetant 45 mg. For VMS severity, least squares mean difference for fezolinetant versus placebo was −0.24 (95% CI, −0.35 to −0.13) for the 45-mg dose.

The four coprimary endpoints were met, with data demonstrating that fezolinetant 30 and 45 mg provided statistically significant improvements in mean daily VMS frequency and severity at weeks 4 and 12 compared with placebo. An additional 52-week randomized phase 3 trial, SKYLIGHT 4 (NCT04003389), confirmed the safety and tolerability of fezolinetant.[21]

The objective of these analyses was to further characterize the efficacy of fezolinetant for the treatment of moderate-to-severe VMS due to menopause using responder analysis of VMS frequency and other PRO measures. A further objective used validated methodology to investigate whether the observed efficacy, not adjusted for placebo, resulted in clinically meaningful within-patient changes. Validated methodologies were used to obtain clinically meaningful thresholds (CMT) to determine the within-patient meaningful change across a number of the outcome measures. These analyses were prespecified and used pooled data from SKYLIGHT 1 and 2 (Supplemental Digital Content, http://links.lww.com/MENO/B226).

METHODS

Study design and participants

Clinical trial methodology, including detailed inclusion/exclusion criteria of these two phase 3, randomized, double-blind, placebo-controlled studies (SKYLIGHT 1 and SKYLIGHT 2), have been published.[19,20] Briefly, eligible participants were born female, aged ≥40 to ≤65 years, and seeking treatment or relief from moderate-to-severe VMS, defined as a minimum average of seven hot flashes per day. Participants were initially randomized to once-daily fezolinetant 30 mg, fezolinetant 45 mg, or placebo (1:1:1) for 12 weeks. A 40-week extension followed, in which all participants received active treatment (individuals initially randomized to placebo were rerandomized to fezolinetant 30 or 45 mg).

The study protocols were approved by institutional review boards/independent ethics committees and were conducted in accordance with the Declaration of Helsinki and International Council for Harmonization Good Clinical Practice Guidelines. All participants provided written informed consent.

Outcome measures

The current manuscript reports the results of responder analyses from SKYLIGHT 1 and SKYLIGHT 2. The four coprimary endpoints in SKYLIGHT 1 and SKYLIGHT 2 were mean change in daily frequency and severity of moderate-to-severe VMS from baseline to weeks 4 and 12. Daily VMS data were collected using an electronic VMS diary, completed daily during a 24-hour period by participants from screening through to the follow-up visit. The VMS diary, an interactive electronic data capture system available for data entry 24 hours per day in real time or retrospectively, included a reference guide with the following definitions: mild symptoms (ie, sensation of heat without sweating); moderate symptoms (ie, sensation of heat with

Authors' contributions: M.B., M.E., L.S., F.D.O., A.M., and E.S. did the study design. K.A.J. was a study investigator. K.A.J. enrolled participants. K.A.J., M.B., M.E., L.S., F.D.O., A.M., and E.S. did the collection and assembly of data, including data management. K.A.J., M.B., M.E., L.S., F.D.O, A.M., and E.S. did the data analysis. All authors did the data interpretation, manuscript preparation, manuscript review and revisions, as well as final approval of the manuscript.

Supplemental digital content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's Website (www.menopause.org).

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sweating, able to continue activity); and severe symptoms (ie, sensation of heat with sweating, causing cessation of activity).

The PRO as defined for these analyses included the Patient-Reported Outcomes Measurement Information System Sleep Disturbance–Short Form (PROMIS SD SF) 8b Total Score, Menopause-Specific Quality of Life (MENQoL) Total Score, and MENQoL VMS Domain Score.

The PROMIS is a set of patient-centered instruments used to evaluate physical, mental, and social health.[22] The PROMIS SD SF 8b, developed from the PROMIS instrument as a sleep disturbance assessment, is validated for measuring the impact of menopause-associated VMS symptoms.[23] The instrument evaluates difficulties and concerns with falling asleep, staying asleep, and getting enough sleep, as well as perceptions on the quality and satisfaction of sleep over the past 7 days. Total score is calculated by summing the items (range 8-40; higher scores represent more disturbed sleep). If some items were not completed, the score was considered missing.

The MENQoL is a validated self-administered questionnaire consisting of 29 items within four domains of menopausal symptoms (vasomotor, psychosocial, physical, and sexual).[24] Items are rated as present (scored as 2) or not present (scored as 1) in the previous month. When present, each item is further graded using a Likert scale of 0 (not bothersome) to 6 (extremely bothersome); thus, each item has a total possible score of 1 to 8. The mean score for the items in each domain is then calculated, with higher scores representing poorer HRQoL.

Definitions of response

Responder analyses were performed using two different approaches. The first approach defined a responder as a participant who experienced a reduction in the frequency of VMS of ≥50%, ≥75%, ≥90%, or 100% from baseline to weeks 4 and 12. The second approach for categorizing responders used PRO measures to evaluate the proportion of participants achieving a clinically meaningful within-patient change (not placebo adjusted) at week 4 and 12 compared with baseline in one, two, or three outcomes. Single responders were the percentage of women achieving a clinically meaningful response in either VMS frequency, PROMIS SD SF 8b, MENQoL Total Score, or MENQoL Domain Score. The double and triple responder analyses combined VMS frequency plus one or more of the PRO. Double responders were the percentage of women achieving a clinically meaningful response in VMS frequency plus one of the following PRO: MENQOL Total Score, MENQOL VMS Domain Score, or PROMIS SD SF 8b Score. Triple responders were the percentage of women achieving a clinically meaningful response in VMS frequency plus two of the PRO. Using pooled data from SKYLIGHT 1 and SKYLIGHT 2, Patient Global Impression of Change (PGI-C) VMS was deemed a suitable anchor measure for meaningful within-patient change in VMS frequency.

The CMT were determined using anchor-based (primary approach) and distribution-based (supportive analyses) methods (Supplemental Table 1, Supplemental Digital Content, http://links.lww.com/MENO/B227). Thresholds were 8.00 for the PROMIS SD SF 8b Score, 0.90 for the MENQoL Total Score, and 2.0 for the MENQoL VMS Domain Score. The methodological approach used to derive the relevant thresholds for within-patient meaningful reduction in frequency of VMS will be published separately. In brief, VMS frequency data were anchored to PGI-C VMS data. The PGI-C VMS asked the following question: "Compared to the beginning of this study, how would you rate your hot flushes/night sweats now?" Participants rated change using a seven-point Likert scale: "much better," "moderately better," "a little better," "no change," "a little worse," "moderately worse," and "much worse." Patient responses for PGI-C VMS were collected at weeks 4 and 12. The anchor level for meaningful within-patient change in PGI-C VMS was "moderately better." Thresholds for a meaningful within-patient change in moderate-to-severe VMS frequency were estimated to be a reduction of 5.73 and 6.20 VMS episodes per day at week 4 and 12, respectively.

Subgroup analysis

To identify patients who could potentially benefit most from treatment with fezolinetant, participants were allocated into various subgroups according to demographics and VMS history. For demographics, subgroups were defined according to age at baseline (≥40 to <45, ≥45 to <50, ≥50 to <55, ≥55 to <60, and ≥60 y) and body mass index (BMI) at baseline (<25, ≥25 to <30, ≥30 to <35, and ≥35 kg/m^2). For VMS history, subgroups were defined according to time since onset of VMS and severity of VMS (moderate and severe) at baseline.

Statistical analyses

SKYLIGHT 1 and SKYLIGHT 2 were designed so that the family-wise type I error rate was controlled using the Hochberg approach for all the comparisons of active dose groups with placebo for the coprimary efficacy endpoints, namely, mean change from baseline to weeks 4 and 12 in frequency and severity of moderate-to-severe VMS. The current pooled analyses do not control the type I error rate, that is, without multiplicity adjustment, so *P* values do not confer statistical significance. Rather, the *P* values are considered indicative, and not confirmatory, and have been used for the purposes of hypothesis generation.

For change in the frequency of moderate and severe VMS from baseline to week 4 and week 12, a mixed-model repeated measures model was used, with treatment group, week (week 1 through week 12), smoking status (current vs former/never), and study (SKYLIGHT 1 vs SKYLIGHT 2) as factors, with baseline weight and baseline measurement as covariates, as well as an interaction of treatment by week and an interaction of baseline measurement by week. The PROMIS SD SF 8b and MENQoL Total and Domain Scores were analyzed using a mixed-model repeated measures model, with clinically meaningful change from baseline as the dependent variable; treatment group, week (week 1 through week 12), and smoking status (current vs former/never) as factors; and baseline weight and baseline measurement as covariates, as well as an interaction of treatment by week and an interaction of baseline measurement by week. The relative treatment effects in VMS frequency and VMS severity at weeks 4 and 12 are presented as least squares mean estimates with 95% CI.

Single responder analyses were performed using logistic regression from both the anchor and distribution-based CMT. The logistic regression models included study (SKYLIGHT 1 vs SKYLIGHT 2), treatment group, and smoking status (current vs former/never) as factors for PGI-C VMS and PGI-C Sleep Disturbance; study (SKYLIGHT 1 vs SKYLIGHT 2), treatment group, and smoking status (current vs former/never) as factors; and baseline as covariate for PROMIS SD SF 8b and MENQoL Total and Domain Scores. The odds ratio (OR; fezolinetant over placebo) and associated two-sided 95% CI were determined for the double and triple responder analyses; differences were considered statistically significant when the 95% CI did not include zero.

RESULTS

Study participants

A total of 1,022 women were randomized and received at least one dose of study drug (placebo, n = 342; fezolinetant 30 mg, n = 339; fezolinetant 45 mg, n = 341) (Table 1). Mean (standard deviation) age was 54.3 (5.0) years and most women were White (828 [81.1%]). In total, 243 of 1,022 (23.8%) were Hispanic or Latina. Demographic data were largely balanced across groups, although mean time since onset of hot flashes was slightly longer in the placebo group (81.9 mo) versus the fezolinetant 30 mg (76.7 mo) and 45 mg (76.9 mo) groups.

Coprimary endpoints

As previously reported,[19,20] fezolinetant 30 mg and 45 mg provided statistically significant improvements in mean daily VMS frequency and severity at weeks 4 and 12 compared with placebo (Supplemental Table 2, Supplemental Digital Content, http://links.lww.com/MENO/B227).

Responder analyses

A greater proportion of participants had a ≥50%, ≥75%, or ≥90% reduction in the frequency of moderate-to-severe VMS from baseline to weeks 4 and 12 in the fezolinetant 45 mg group than in the placebo group (Fig. 1). At week 4, a ≥50%, ≥75%, or ≥90% reduction in VMS frequency from baseline was achieved by 53%, 30%, and 16% of the fezolinetant 45 mg group, respectively, compared with 27%, 14%, and 6% of the placebo group, respectively. Therefore, there was an absolute reduction of 23%, 20%, and 14% in the fezolinetant 45 mg group versus placebo. Furthermore, a greater proportion of participants randomized to fezolinetant had a 100% reduction in VMS frequency from baseline (7% of the fezolinetant 45 mg group compared with 2% of the placebo group). Similarly, at week 12, a ≥50%, ≥75%, or ≥90% reduction in moderate-to-severe VMS frequency from baseline was achieved by 59%, 37%, and 23% of the fezolinetant 45 mg group, respectively, compared with 36%, 17%, and 9% of the placebo group, respectively. A 100% reduction from baseline in VMS frequency was achieved by 13% of the fezolinetant 45 mg group compared with 4% of the placebo group (so an absolute reduction of 9% in the fezolinetant 45 mg group vs placebo).

Improvements for the 30 mg dose were similar to those for 45 mg: at week 4, a ≥50%, ≥75%, or ≥90% reduction in VMS frequency from baseline was achieved by 47%, 29%, and 12% of the fezolinetant 30 mg group, respectively, and a 100% reduction from baseline in VMS frequency was achieved by 5% of the

TABLE 1. *Key participant demographics and baseline characteristics (FAS)*

Parameter	Placebo (n = 342)	Fezolinetant 45 mg (n = 341)	Fezolinetant 30 mg (n = 339)	Total (N = 1,022)
Ethnicity[a], *n* (%)				
Not Hispanic or Latina	262 (77.1)	252 (73.9)	263 (77.6)	777 (76.2)
Hispanic or Latina	78 (22.9)	89 (26.1)	76 (22.4)	243 (23.8)
Race[b], *n* (%)				
American Indian or Alaska Native, Asian, other[c]	7 (2.0)	8 (2.3)	4 (1.2)	19 (1.9)
Black or African American	59 (17.3)	59 (17.3)	56 (16.6)	174 (17.0)
White	276 (80.7)	274 (80.4)	278 (82.2)	828 (81.1)
Age, mean (SD), y	54.7 (4.7)	54.3 (5.3)	54.0 (4.9)	54.3 (5.0)
Weight, mean (range), kg	74.49 (46.2-125.0)	75.17 (45.0-110.6)	75.18 (42.0-121.2)	74.95 (42.0-125.0)
BMI[d], mean (range), kg/m^2	28.17 (18.6-38.0)	28.12 (18.0-37.9)	28.02 (18.0-37.8)	28.10 (18.0-38.0)
Current smoker, *n* (%)	57 (16.7)	57 (16.7)	55 (16.2)	169 (16.5)
Time since onset of VMS, mean (range), mo	81.9 (2-422)	76.9 (1-396)	76.7 (3-370)	78.5 (1-422)
Amenorrhea, *n* (%)				
No	13 (3.8)	7 (2.1)	7 (2.1)	27 (2.6)
Yes	329 (96.2)	334 (97.9)	332 (97.9)	995 (97.4)
Hysterectomy, *n* (%)				
No	240 (70.2)	227 (66.6)	226 (66.7)	693 (67.8)
Yes	102 (29.8)	114 (33.4)	113 (33.3)	329 (32.2)
Oophorectomy, *n* (%)				
No	267 (78.1)	265 (77.7)	269 (79.4)	801 (78.4)
Yes	75 (21.9)	76 (22.3)	70 (20.6)	221 (21.6)

Data are shown for the FAS (all participants who were randomized and received at least one dose of study intervention).
BMI, body mass index; FAS, full analysis set; SD, standard deviation; VMS, vasomotor symptoms.
[a]Data on ethnicity were missing for two participants in the placebo (and total) group.
[b]Data on race were missing for one participant in the fezolinetant 30 mg (and total) group.
[c]More than one race.
[d]Data on BMI were missing for one participant in the fezolinetant 45 mg (and total) group.

fezolinetant 30 mg group. At week 12, a ≥50%, ≥75%, ≥90%, or 100% reduction in moderate-to-severe VMS frequency from baseline was achieved by 47%, 32%, 17%, and 8% of the fezolinetant 30 mg group, respectively. Odds ratios for both fezolinetant groups versus placebo for all response categories were >1 and therefore supportive of a beneficial effect for both fezolinetant treatment groups.

Responders with a ≥50% reduction in VMS frequency from baseline to week 12, stratified by age, BMI, time since onset of VMS, and VMS severity at baseline, are presented in Tables 2 and 3. Across all subgroups, the proportion of responders was consistently greater in both the fezolinetant 45 and 30 mg groups compared with placebo, and the OR were >1, supportive of a beneficial effect for fezolinetant.

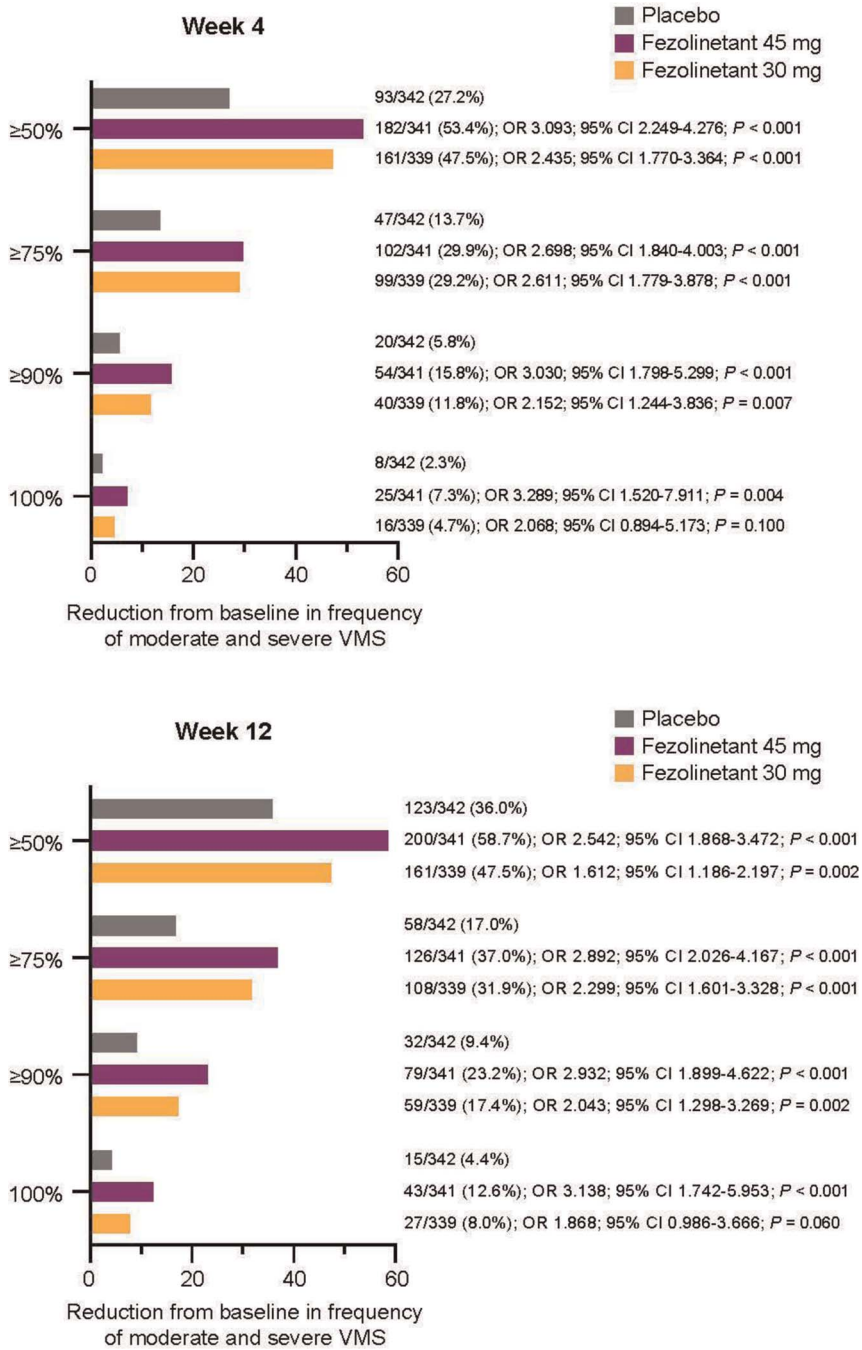

FIG. 1. Proportions of participants with >50%, >75%, >90%, and >100% reduction in moderate-to-severe VMS from baseline to weeks 4 and 12. Odds ratios, 95% CI, and unadjusted *P* values are based on logistic regression, with treatment group, study protocol, and smoking status (current vs former/never) as factors, and mean frequency of VMS at baseline as a covariate. An OR of >1 indicates a favorable response in the fezolinetant group. CI, confidence interval; OR, odds ratio; VMS, vasomotor symptoms.

TABLE 2. *Percentage of responders with a ≥50% reduction in moderate and severe VMS frequency from baseline at week 12, stratified by age and BMI*

Statistics	Placebo (n = 342)	Fezolinetant 45 mg (n = 341)	Fezolinetant 30 mg (n = 339)
Age, y			
≥40 to <45			
Percentage of responders (n/N)	20.0 (1/5)	50.0 (7/14)	55.6 (5/9)
OR: fezolinetant vs placebo	—	4.953	5.080
95% two-sided CI	—	0.377-140.822	0.382-141.155
≥45 to <50			
Percentage of responders (n/N)	33.3 (14/42)	56.1 (23/41)	48.1 (25/52)
OR: fezolinetant vs placebo	—	2.301	1.835
95% two-sided CI	—	0.935-5.817	0.775-4.454
≥50 to <55			
Percentage of responders (n/N)	36.1 (48/133)	59.7 (74/124)	43.2 (54/125)
OR: fezolinetant vs placebo	—	2.743	1.359
95% two-sided CI	—	1.653-4.605	0.821-2.258
≥55 to <60			
Percentage of responders (n/N)	36.4 (36/99)	58.1 (61/105)	51.5 (53/103)
OR: fezolinetant vs placebo	—	2.368	1.817
95% two-sided CI	—	1.350-4.202	1.035-3.218
≥60			
Percentage of responders (n/N)	38.1 (24/63)	61.4 (35/57)	50.0 (25/50)
OR: fezolinetant vs placebo	—	2.454	1.703
95% two-sided CI	—	1.158-5.304	0.780-3.759
BMI, kg/m^2			
<25			
Percentage of responders (n/N)	38.1 (37/97)	57.5 (50/87)	53.8 (57/106)
OR: fezolinetant vs placebo	—	2.173	1.817
95% two-sided CI	—	1.197-3.990	1.029-3.237
≥25 to <30			
Percentage of responders (n/N)	36.1 (48/133)	59.2 (90/152)	43.2 (51/118)
OR: fezolinetant vs placebo	—	2.539	1.328
95% two-sided CI	—	1.575-4.130	0.798-2.216
≥30 to <35			
Percentage of responders (n/N)	28.2 (22/78)	58.3 (42/72)	46.3 (38/82)
OR: fezolinetant vs placebo	—	3.563	2.193
95% two-sided CI	—	1.813-7.178	1.141-4.290
≥35			
Percentage of responders (n/N)	47.1 (16/34)	58.6 (17/29)	48.5 (16/33)
OR: fezolinetant vs placebo	—	1.917	1.175
95% two-sided CI	—	0.654-5.834	0.434-3.220

Odds ratios, 95% CI, and unadjusted P values are based on logistic regression, with treatment group, study protocol, and smoking status (current vs former/never) as factors, and mean frequency of VMS at baseline as a covariate. An OR of >1 indicates a favorable response in the fezolinetant group.
BMI, body mass index; CI, confidence interval; OR, odds ratio; VMS, vasomotor symptoms.

A greater proportion of responders was observed in the fezolinetant 45 mg group compared with placebo at week 12 in all four single responder analyses (Fig. 2). Response rates by VMS frequency were 55% in the fezolinetant 45 mg group compared with 31% for placebo (so a difference of 24%). In addition, the proportion of responders for the MENQoL VMS Domain were 58% in the fezolinetant 45 mg group versus 41% in the placebo group (so a difference of 17%).

In the double responder analyses, OR were supportive of a beneficial effect for fezolinetant 45 mg compared with placebo. For VMS frequency plus PROMIS SD SF 8b Total Score, the OR was 1.822 for fezolinetant 45 mg; for VMS frequency plus MENQoL Total Score, the OR was 2.367; for VMS frequency plus MENQoL VMS Domain Score, the OR was 2.400 (Fig. 2). Similarly, beneficial effects were observed for triple responders based on VMS frequency and PROMIS SD SF 8b Total Score plus MENQoL Total Score (OR, 1.903), and plus MENQoL VMS Domain Score (OR, 1.982) (Fig. 2).

A greater proportion of single and double responders were also seen for fezolinetant 30 mg versus placebo: response rates for VMS frequency and the MENQoL VMS Domain were 50% and 56%, respectively, and OR were 1.930 for VMS frequency plus PROMIS SD SF 8b Total Score, 1.853 for VMS frequency plus MENQoL Total Score, and 1.960 for VMS frequency plus MENQoL VMS Domain Score. Similarly, beneficial effects were observed for triple responders based on VMS frequency and PROMIS SD SF 8b Total Score plus MENQoL Total Score (OR, 1.882) and plus MENQoL VMS Domain Score (OR, 1.976) (Fig. 2).

DISCUSSION

Vasomotor symptoms are bothersome and have a negative impact on women's HRQoL, including impact on sleep, concentration, mood, energy, sexual activity, and work/leisure activities.[5,6] In this prespecified analysis using pooled data from SKYLIGHT 1 and 2, treatment with fezolinetant not only reduced the frequency and severity of VMS on the previously reported primary endpoints[19,20] but also resulted in higher responder rates based on within-patient changes in PRO. The data also show that

improvements in VMS frequency with fezolinetant are associated with improvements in PRO measures of VMS.

In the current analysis, a ≥50% reduction (within-patient change) in VMS frequency at week 12 was achieved by 23% and 11% more participants receiving fezolinetant 45 and 30 mg, respectively, versus the placebo group. Subgroup analyses showed that this effect was observed irrespective of age and BMI. In addition, 8% and 4% more participants receiving fezolinetant 45 and 30 mg, respectively, versus those receiving placebo experienced a 100% reduction in the frequency of moderate-to-severe VMS from baseline to week 12. These proportions were lower than those observed for a ≥50% reduction, but a 100% reduction in the frequency in VMS appears to be a challengingly high target.

Consistent with the individual study data, response was observed for a proportion of placebo-treated patients, albeit at a lower rate than those receiving fezolinetant. Robust responses to placebo treatment have been observed in randomized trials for VMS treatment.[25-27] In the absence of no-treatment arms, it is unclear whether the benefits with placebo reflect nonspecific effects, natural history, or statistical phenomena.[26,27]

Between-group difference is expected to inform the statistical significance between outcomes experienced by patients randomized to fezolinetant versus those randomized to placebo, but this finding will not indicate whether individual patients have experienced a meaningful clinical benefit.[28] To aid the interpretation of data, our study used a range of appropriate thresholds[29] that would constitute a clinically meaningful within-patient change from the patient perspective (ie, individual patient level), across several PRO endpoints. Substantially more participants in the fezolinetant 45 and 30 mg treatment groups compared with placebo experienced a clinically meaningful change based on the results of all the single, double, and triple responder analyses (ie, a clinically meaningful change in either VMS frequency, MENQOL Total Score, MENQOL VMS Domain Score, or PROMIS SD SF 8b Score [single responders], or in VMS frequency plus one [double responders] or two [triple responders] of the following PRO: MENQOL Total Score, MENQOL VMS Domain Score, or PROMIS SD SF 8b Score). The OR were >1 in the three double (range, 1.822-2.400) and two triple (range, 1.882-1.982) responder analyses.

Other publications have assessed clinically or minimally important differences in postmenopausal women with moderate/severe VMS, but they involved different treatments and anchored with different PRO measures compared with our study, so direct comparisons cannot be made. In two studies of hormone therapy, weekly VMS severity[30] or weekly VMS frequency[31] were anchored to CGI outcomes (these were generic rather than specific to VMS). Other reports of responder thresholds in moderate-to-severe VMS include VMS frequency anchored to CGI and the MENQoL in women treated with hormone therapy[32];

TABLE 3. *Percentage of responders with a ≥50% reduction in moderate and severe VMS frequency from baseline at week 12, stratified by time since onset of VMS and VMS severity at baseline*

Statistics	Placebo (*n* = 342)	Fezolinetant 45 mg (*n* = 341)	Fezolinetant 30 mg (*n* = 339)
Time since onset of VMS			
1st quartile			
Percentage of responders (*n*/*N*)	36.1 (30/83)	65.5 (57/87)	54.7 (47/86)
OR: fezolinetant vs placebo	—	3.458	2.073
95% two-sided CI	—	1.843-6.622	1.117-3.891
2nd quartile			
Percentage of responders (*n*/*N*)	34.6 (28/81)	54.2 (45/83)	49.5 (45/91)
OR: fezolinetant vs placebo	—	2.181	1.817
95% two-sided CI	—	1.159-4.159	0.976-3.421
3rd quartile			
Percentage of responders (*n*/*N*)	31.0 (27/87)	51.1 (45/88)	42.0 (34/81)
OR: fezolinetant vs placebo	—	2.387	1.582
95% two-sided CI	—	1.284-4.510	0.839-3.009
4th quartile			
Percentage of responders (*n*/*N*)	41.8 (38/91)	63.9 (53/83)	44.4 (36/81)
OR: fezolinetant vs placebo	—	2.389	1.109
95% two-sided CI	—	1.298-4.459	0.602-2.043
Severity of moderate and severe VMS at baseline			
Group 1			
Percentage of responders (*n*/*N*)	36.6 (63/172)	58.0 (102/176)	52.1 (85/163)
OR: fezolinetant vs placebo	—	2.416	1.967
95% two-sided CI	—	1.564-3.758	1.266-3.076
Group 2			
Percentage of responders (*n*/*N*)	35.3 (60/170)	59.4 (98/165)	43.8 (77/176)
OR: fezolinetant vs placebo	—	2.680	1.421
95% two-sided CI	—	1.727-4.192	0.922-2.198

First quartile, time since onset of VMS of ≤787.0 days; second quartile, time since onset of VMS of >787.0 to ≤1,701.5 days; third quartile, time since onset of VMS >1,701.5 days to ≤3,344.0 days; fourth quartile, time since onset of VMS >3,344.0 days. Group 1, severity of moderate and severe VMS at baseline <2.36; group 2, severity of moderate and severe VMS at baseline ≥2.36. Odds ratios, 95% CI, and unadjusted *P* values are based on logistic regression, with treatment group, study protocol, and smoking status (current vs former/never) as factors, and mean frequency of VMS at baseline as a covariate. An OR of >1 indicates a favorable response in the fezolinetant group.

CI, confidence interval; OR, odds ratio; VMS, vasomotor symptoms.

VMS frequency and severity anchored to the Menopause Symptoms Treatment Satisfaction Questionnaire in women treated with desvenlafaxine[33]; and VMS frequency anchored to the Hot Flash Related Daily Interference scale/Hot Flash Interference scale in women treated with escitalopram.[34]

The results of the responder analyses show that the significant reduction in the frequency and severity of VMS at 12 weeks translated into improvements in HRQoL, as measured by both condition-specific and generic PRO measures. In the individual SKYLIGHT 1 and 2 studies, statistically significant improvements from baseline in MENQoL Total Score and VMS Domain were observed at weeks 4 and 12 in participants treated with fezolinetant 45 and 30 mg versus placebo.[19,20] Improvements in sleep as measured by the PROMIS SD SF 8b were also observed in both individual studies. Although it did not assess fezolinetant at a dose of 45 mg, responder rate was also a key secondary outcome in the fezolinetant phase 2b study,[18] in which participants who received fezolinetant were 3.2 to 12.7 times as likely to achieve a 50% reduction in moderate or severe VMS at the end of treatment compared with placebo,[18] with a

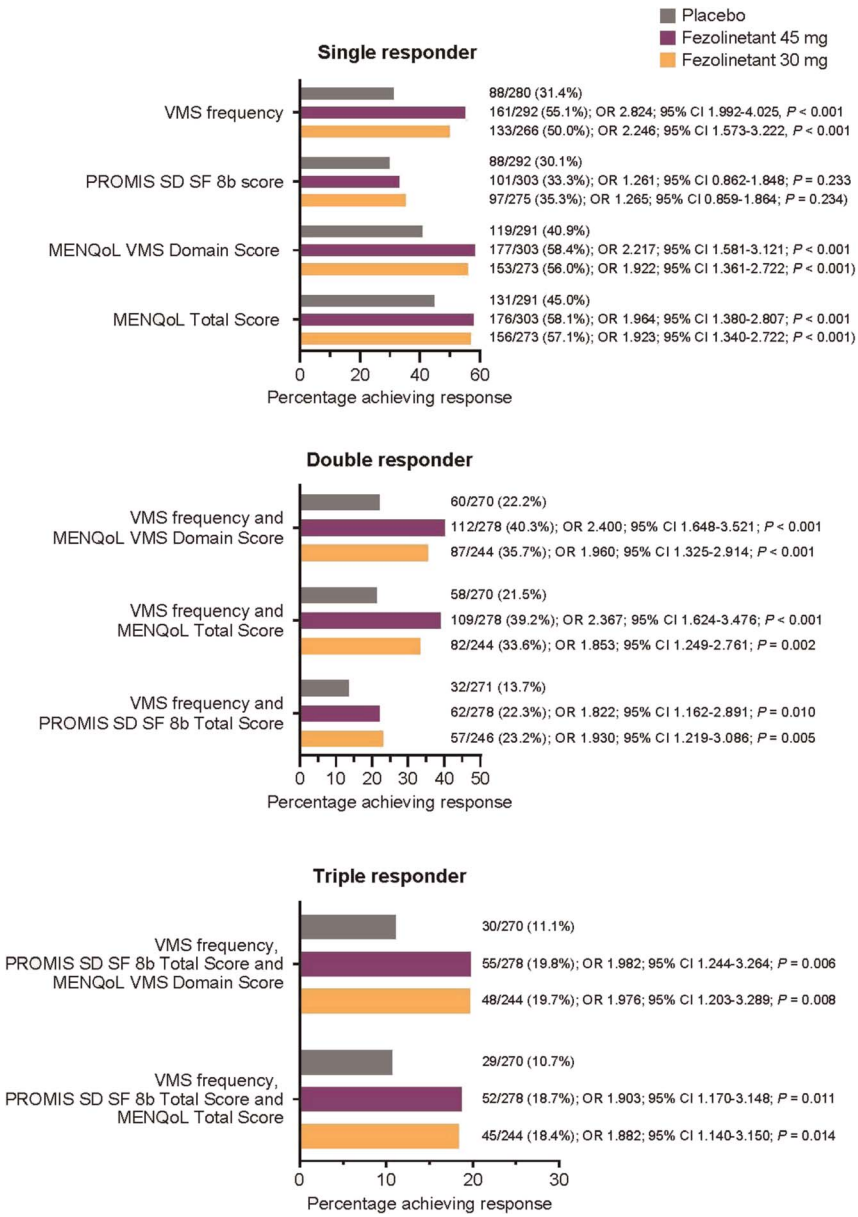

FIG. 2. Proportion of participants responding to combined outcome measures at week 12. Odds ratios, 95% CI, and unadjusted *P* values are based on logistic regression, with treatment group, study protocol, and smoking status (current vs former/never) as factors, and mean frequency of VMS at baseline as a covariate. An OR of >1 indicates a favorable response in the fezolinetant group. The responders used in the model for single responder, VMS frequency, were based on observed cases (placebo 88/279, fezolinetant 45 mg 161/291, fezolinetant 30 mg 132/264). CI, confidence interval; MENQoL, Menopause-Specific Quality of Life; OR, odds ratio; PROMIS SD SF 8b, Patient-Reported Outcomes Measurement Information System Sleep Disturbance–Short Form 8b; VMS, vasomotor symptoms.

higher proportion of fezolinetant-treated participants experiencing a ≥50%, 70%, or 90% reduction in moderate or severe VMS frequency versus placebo.[35]

Menopausal hormone therapy is an effective treatment option for VMS, but nonhormone treatment options are under investigation for women who cannot take or choose not to take hormone therapy. Non-FDA–approved medications that have been shown to have efficacy against VMS include clonidine, gabapentin, selective serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors. Fezolinetant and low-dose paroxetine are currently the only nonhormone treatments approved by the US Food and Drug Administration for the treatment of VMS,[36] but several other potential nonhormone options are undergoing late-stage clinical development.[37,38]

A key strength of the present study is the inclusion of a large participant population (n = >1,000) from two randomized, double-blind, placebo-controlled trials. Other strengths include that the study duration was consistent with other clinical trials in VMS,[39–41] because the inclusion of placebo for long periods is difficult from a patient perspective, and the use of MENQoL Total Score, which captures multiple HRQoL aspects (vasomotor, psychosocial, physical, and sexual function).

A limitation is that this analysis was restricted to 12 weeks, due to the 12-week duration of the placebo-controlled period in the original studies. Additional data of interest may have been uncovered if a longer placebo-controlled period had been employed.

CONCLUSIONS

Vasomotor symptoms are bothersome and can negatively impact HRQoL, including effects on sleep, concentration, mood, energy, sexual activity, and work/leisure activities. This analysis further characterizes the efficacy of fezolinetant for the treatment of moderate-to-severe VMS due to menopause using a distinctive approach to assess outcomes from the SKYLIGHT 1 and SKYLIGHT 2 trials. Fezolinetant was associated with a significantly higher within-patient clinically meaningful improvement in important quality-of-life measures, including VMS frequency, PROMIS SD SF 8b Total Score, MENQoL Total Score, and MENQoL VMS Domain Score. Overall, the data provide further evidence of the utility of fezolinetant as a nonhormone treatment option for women experiencing VMS due to menopause. Increased emphasis on the clinically meaningful benefit experienced by women with treatment can facilitate meaningful dialog between clinicians and patients.

Acknowledgments: We thank Randall H. Bender, Jia Ma, Elise Bruce, and Lori McLeod of RTI-HS and Stephanie Rhoten of IQVIA for data analysis.

REFERENCES

1. Gold EB, Colvin A, Avis N, et al. Longitudinal analysis of the association between vasomotor symptoms and race/ethnicity across the menopausal transition: study of women's health across the nation. *Am J Public Health* 2006;96:1226-1235. doi: 10.2105/AJPH.2005.066936
2. Thurston RC, Joffe H. Vasomotor symptoms and menopause: findings from the Study of Women's Health across the Nation. *Obstet Gynecol Clin North Am* 2011;38:489-501. doi: 10.1016/j.ogc.2011.05.006
3. Freeman EW, Sammel MD, Sanders RJ. Risk of long-term hot flashes after natural menopause: evidence from the Penn Ovarian Aging Study cohort. *Menopause* 2014;21:924-932. doi: 10.1097/GME.0000000000000196
4. Avis NE, Crawford SL, Greendale G, et al, Study of Women's Health Across the Nation. Duration of menopausal vasomotor symptoms over the menopause transition. *JAMA Intern Med* 2015;175:531-539. doi: 10.1001/jamainternmed.2014.8063
5. Williams RE, Levine KB, Kalilani L, Lewis J, Clark RV. Menopause-specific questionnaire assessment in US population-based study shows negative impact on health-related quality of life. *Maturitas* 2009;62:153-159. doi: 10.1016/j.maturitas.2008.12.006
6. Nappi RE, Kroll R, Siddiqui E, et al. Global cross-sectional survey of women with vasomotor symptoms associated with menopause: prevalence and quality of life burden. *Menopause* 2021;28:875-882. doi: 10.1097/GME.0000000000001793
7. El Khoudary SR, Greendale G, Crawford SL, et al. The menopause transition and women's health at midlife: a progress report from the Study of Women's Health Across the Nation (SWAN). *Menopause* 2019;26:1213-1227. doi: 10.1097/GME.0000000000001424
8. Thurston RC, Aslanidou Vlachos HE, Derby CA, et al. Menopausal vasomotor symptoms and risk of incident cardiovascular disease events in SWAN. *J Am Heart Assoc* 2021;10:e017416. doi: 10.1161/JAHA.120.017416
9. Biglia N, Cagnacci A, Gambacciani M, Lello S, Maffei S, Nappi RE. Vasomotor symptoms in menopause: a biomarker of cardiovascular disease risk and other chronic diseases? *Climacteric* 2017;20:306-312. doi: 10.1080/13697137.2017.1315089
10. Nappi RE, Chedraui P, Lambrinoudaki I, Simoncini T. Menopause: a cardiometabolic transition. *Lancet Diabetes Endocrinol* 2022;10:442-456. doi: 10.1016/S2213-8587(22)00076-6
11. Astellas Pharma US. Prescribing information for fezolinetant. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216578s000lbl.pdf. Accessed May 16, 2023.
12. European Medicines Agency. Veoza. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/veoza. Accessed March 4, 2024.
13. Rance NE, Dacks PA, Mittelman-Smith MA, Romanovsky AA, Krajewski-Hall SJ. Modulation of body temperature and LH secretion by hypothalamic KNDy (kisspeptin, neurokinin B and dynorphin) neurons: a novel hypothesis on the mechanism of hot flushes. *Front Neuroendocrinol* 2013;34:211-227. doi: 10.1016/j.yfrne.2013.07.003
14. Archer DF, Sturdee DW, Baber R, et al. Menopausal hot flushes and night sweats: where are we now? *Climacteric* 2011;14:515-528. doi: 10.3109/13697137.2011.608596
15. Depypere H, Lademacher C, Siddiqui E, Fraser GL. Fezolinetant in the treatment of vasomotor symptoms associated with menopause. *Expert Opin Investig Drugs* 2021;30:681-694. doi: 10.1080/13543784.2021.1893305
16. Depypere H, Timmerman D, Donders G, et al. Treatment of menopausal vasomotor symptoms with fezolinetant, a neurokinin 3 receptor antagonist: a phase 2a trial. *J Clin Endocrinol Metab* 2019;104:5893-5905. doi: 10.1210/jc.2019-00677
17. Fraser GL, Hoveyda HR, Clarke IJ, et al. The NK3 receptor antagonist ESN364 interrupts pulsatile LH secretion and moderates levels of ovarian hormones throughout the menstrual cycle. *Endocrinology* 2015;156:4214-4225. doi: 10.1210/en.2015-1409
18. Fraser GL, Lederman S, Waldbaum A, et al. A phase 2b, randomized, placebo-controlled, double-blind, dose-ranging study of the neurokinin 3 receptor antagonist fezolinetant for vasomotor symptoms associated with menopause. *Menopause* 2020;27:382-392. doi: 10.1097/GME.0000000000001510
19. Lederman S, Ottery FD, Cano A, et al. Fezolinetant for treatment of moderate-to-severe vasomotor symptoms associated with menopause (SKYLIGHT 1): a phase 3 randomised controlled study. *Lancet* 2023;401:1091-1102. doi: 10.1016/S0140-6736(23)00085-5
20. Johnson KA, Martin N, Nappi RE, et al. Efficacy and safety of fezolinetant in moderate-to-severe vasomotor symptoms associated with menopause: a phase 3 RCT. *J Clin Endocrinol Metab* 2023;108:1981-1997. doi: 10.1210/clinem/dgad058
21. Neal-Perry G, Cano A, Lederman S, et al. Safety of fezolinetant for vasomotor symptoms associated with menopause: a randomized controlled trial. *Obstet Gynecol* 2023;141:737-747. doi: 10.1097/AOG.0000000000005114
22. Health Measures. PROMIS®. Available at: https://www.healthmeasures.net/explore-measurement-systems/promis. Accessed January 31, 2023.
23. English M, Stoykova B, Slota C, et al. Qualitative study: burden of menopause-associated vasomotor symptoms (VMS) and validation of PROMIS Sleep Disturbance and Sleep-Related Impairment measures for assessment of

VMS impact on sleep. *J Patient Rep Outcomes* 2021;5:37. doi: 10.1186/s41687-021-00289-y
24. Hilditch JR, Lewis J, Peter A, et al. A menopause-specific quality of life questionnaire: development and psychometric properties. *Maturitas* 1996; 24:161-175. doi: 10.1016/s0378-5122(96)82006-8
25. Zhou T. Estimation of placebo effect in randomized placebo-controlled trials for moderate or severe vasomotor symptoms: a meta-analysis. *Menopause* 2023;30:5-10. doi: 10.1097/GME.0000000000002094
26. Freeman EW, Ensrud KE, Larson JC, et al. Placebo improvement in pharmacologic treatment of menopausal hot flashes: time course, duration, and predictors. *Psychosom Med* 2015;77:167-175. doi: 10.1097/PSY.0000000000000143
27. Pan Y, Meister R, Lowe B, et al. Non-concealed placebo treatment for menopausal hot flushes: study protocol of a randomized-controlled trial. *Trials* 2019;20:508. doi: 10.1186/s13063-019-3575-1
28. U.S. Food & Drug Administration. Patient-focused drug development guidance public workshop. Incorporating clinical outcome assessments into endpoints for regulatory decision-making. Available at: https://www.fda.gov/media/132505/download. Accessed April 17, 2023.
29. Santoro N, Nappi RE, Neal-Perry G, English M, King DD, Yamaguchi Y. Fezolinetant treatment of moderate-to-severe vasomotor symptoms due to menopause: effect of intrinsic and extrinsic factors in two phase 3 studies (SKYLIGHT 1 and 2). *Menopause* 2024;31:247-257. doi: 10.1097/GME.0000000000002340
30. Constantine GD, Simon JA, Kaunitz AM, et al. TX-001HR is associated with a clinically meaningful effect on severity of moderate to severe vasomotor symptoms in the REPLENISH trial. *Menopause* 2020;27:1236-1241. doi: 10.1097/GME.0000000000001602
31. Gerlinger C, Gude K, Hiemeyer F, Schmelter T, Schafers M. An empirically validated responder definition for the reduction of moderate to severe hot flushes in postmenopausal women. *Menopause* 2012;19:799-803. doi: 10.1097/gme.0b013e31823de8ba
32. Constantine GD, Revicki DA, Kagan R, et al. Evaluation of clinical meaningfulness of estrogen plus progesterone oral capsule (TX-001HR) on moderate to severe vasomotor symptoms. *Menopause* 2019;26:513-519. doi: 10.1097/GME.0000000000001261
33. Wyrwich KW, Spratt DI, Gass M, Yu H, Bobula JD. Identifying meaningful differences in vasomotor symptoms among menopausal women. *Menopause* 2008;15:698-705. doi: 10.1097/gme.0b013e31815f892d
34. Carpenter JS, Bakoyannis G, Otte JL, et al. Validity, cut-points, and minimally important differences for two hot flash-related daily interference scales. *Menopause* 2017;24:877-885. doi: 10.1097/GME.0000000000000871
35. Santoro N, Waldbaum A, Lederman S, et al. Effect of the neurokinin 3 receptor antagonist fezolinetant on patient-reported outcomes in postmenopausal women with vasomotor symptoms: results of a randomized, placebo-controlled, double-blind, dose-ranging study (VESTA). *Menopause* 2020;27:1350-1356. doi: 10.1097/GME.0000000000001621
36. Simon JA, Portman DJ, Kaunitz AM, et al. Low-dose paroxetine 7.5 mg for menopausal vasomotor symptoms: two randomized controlled trials. *Menopause* 2013;20:1027-1035. doi: 10.1097/GME.0b013e3182a66aa7
37. Khan SJ, Kapoor E, Faubion SS, Kling JM. Vasomotor symptoms during menopause: a practical guide on current treatments and future perspectives. *Int J Womens Health* 2023;15:273-287. doi: 10.2147/IJWH.S365808
38. Sahni S, Lobo-Romero A, Smith T. Contemporary non-hormonal therapies for the management of vasomotor symptoms associated with menopause: a literature review. *touchREV Endocrinol* 2021;17:133-137. doi: 10.17925/EE.2021.17.2.133
39. Bouchard P, Panay N, de Villiers TJ, et al. Randomized placebo- and active-controlled study of desvenlafaxine for menopausal vasomotor symptoms. *Climacteric* 2012;15:12-20. doi: 10.3109/13697137.2011.586445
40. Hitchcock CL, Prior JC. Oral micronized progesterone for vasomotor symptoms—a placebo-controlled randomized trial in healthy postmenopausal women. *Menopause* 2012;19:886-893. doi: 10.1097/gme.0b013e318247f07a
41. Simon JA, Anderson RA, Ballantyne E, et al. Efficacy and safety of elinzanetant, a selective neurokinin-1,3 receptor antagonist for vasomotor symptoms: a dose-finding clinical trial (SWITCH-1). *Menopause* 2023;30:239-246. doi: 10.1097/GME.0000000000002138