Fezolinetant for treatment of moderate-to-severe vasomotor symptoms associated with menopause (SKYLIGHT 1): a phase 3 randomised controlled study

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Summary

Background Neurokinin 3 receptor antagonists are potential non-hormonal therapies for the treatment of vasomotor symptoms in menopausal women as options are scarce for those who cannot or do not want to take hormone therapy. Fezolinetant is one of the first non-hormonal neurokinin 3 receptor antagonists in development for the treatment of vasomotor symptoms due to menopause. This study investigated the safety and efficacy of fezolinetant for the treatment of moderate-to-severe vasomotor symptoms associated with menopause.

Methods SKYLIGHT 1 is a randomised, double-blind, placebo-controlled, 12-week, phase 3 trial with a 40-week active treatment extension. This trial was done at 97 facilities across the USA, Canada, Czech Republic, Hungary, Poland, Spain, and the UK. Women aged 40–65 years with an average of seven or more moderate-to-severe hot flashes per day were randomly assigned (1:1:1) to once-daily exact-matched placebo, fezolinetant 30 mg, or fezolinetant 45 mg. Randomisation was done using a web-based interactive response system and investigators, project team members, clinical staff, and participants were masked to treatment assignment. Coprimary endpoints were mean change in frequency and severity of vasomotor symptoms from baseline to weeks 4 and 12. The efficacy and safety analyses comprised all randomly assigned participants who received at least one dose of study drug. This trial is registered with ClinicalTrials.gov (NCT04003155) and is completed.

Findings Between July 11, 2019, and Aug 11, 2021, 2205 women were recruited of whom 175 were assigned to placebo, 176 to fezolinetant 30 mg, and 176 to fezolinetant 45 mg (175 in the placebo group, 174 in the fezolinetant 30 mg group, and 173 in the fezolinetant 45 mg received at least one dose [safety analysis set]). One participant randomly assigned to fezolinetant 45 mg received fezolinetant 30 mg in error, so the efficacy analysis set (full analysis set) consisted of 173 in the fezolinetant 30 mg group and 174 in the fezolinetant 45 mg group. 23 participants in the placebo group, 31 in the fezolinetant 30 mg group, and 13 in the fezolinetant 45 mg group discontinued treatment before week 12, mostly due to adverse events or participant withdrawal. Compared with placebo, fezolinetant 30 mg and fezolinetant 45 mg significantly reduced the frequency of vasomotor symptoms at week 4 (difference in change in least squares mean –1·87 [SE 0·42; p<0·001], –2·07 [SE 0·42; p<0·001]) and week 12 (–2·39 [SE 0·44; p<0·001], –2·55 [SE 0·43; p<0·001]). Compared with placebo, fezolinetant 30 mg and 45 mg significantly reduced the severity of vasomotor symptoms at week 4 (–0·15 [0·06; p=0·012], –0·19 [0·06; p=0·002]) and week 12 (–0·24 [0·08; p=0·002], –0·20 [0·08; p=0·007]). Improvements in frequency and severity of vasomotor symptoms were observed after 1 week and maintained over 52 weeks. During the first 12 weeks, treatment-emergent adverse events occurred in 65 (37%) of 174 women in the fezolinetant 30 mg group, 75 (43%) of 173 in the fezolinetant 45 mg group, and 78 (45%) of 175 in the placebo group. The incidence of liver enzyme elevations was low (placebo n=1; fezolinetant 30 mg n=2; fezolinetant 45 mg n=0) and these events were generally asymptomatic, transient, and resolved while on treatment or after treatment discontinuation.

Interpretation Data support the clinical use of fezolinetant as a non-hormonal treatment for vasomotor symptoms associated with menopause. The study was placebo-controlled for 12 weeks followed by a 40-week blinded extension to assess the maintenance of effect. Furthermore, the population studied was diverse and representative of the potential target population for fezolinetant therapy. Further characterisation of the benefit of fezolinetant on quality of life, including on symptoms of mood and sexual wellbeing, merits investigation.

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Introduction

The burden of vasomotor symptoms characterised by hot flashes (ie, hot flushes or night sweats) in women undergoing menopausal transition is substantial, with up to 80% having vasomotor symptoms.[1] Most women rate vasomotor symptoms as moderate-to-severe,[2] comprising

Research in context

Evidence before this study

Women face a substantial burden of vasomotor symptoms (hot flashes, also called hot flushes or night sweats) during menopausal transition, impacting quality of life, sleep, mood, concentration, and sexual wellbeing. Vasomotor symptoms can start before menopause, continue for more than 10 years, and have been associated with a decline in physical health. Available treatments, such as menopausal hormone therapy and selective serotonin receptor antagonists, are not appropriate for all women. Therefore, an unmet need exists for effective treatment alternatives for vasomotor symptoms in menopausal women. The thermoregulatory centre in the hypothalamus is innervated by kisspeptin–neurokinin B–dynorphin (KNDy) neurons. These neurons are stimulated by the neuropeptide neurokinin B, acting at neurokinin 3 receptors, and inhibited by oestrogen. Declining oestrogen concentrations during menopausal transition alters neurokinin 3 receptor-mediated activation leading to hypertrophy of KNDy neurons and dysregulation of the thermoregulatory centre. The thermoregulatory centre triggers heat dissipation effectors. Vasodilation in the skin causes heat loss, which can trigger hot flashes, sweating, and chills. Neurokinin 3 receptor antagonists, such as fezolinetant, are therefore of interest as potential non-hormonal therapies for treatment of moderate-to-severe vasomotor symptoms associated with menopause. We searched PubMed on March 16, 2022 using the terms "neurokinin 3 receptor" and "vasomotor symptoms or hot flash or hot flush" with an English language modifier only and identified 35 studies. Of these studies, five were animal studies, 16 were review or overview articles, three were comments or editorials, two discussed genetic variation associated with menopause symptoms, and nine were phase 2 or earlier clinical studies that addressed vasomotor symptoms in menopausal women using fezolinetant, MLE4901, SJX-653, or neurokinin B infusion. Fezolinetant phase 2 data supported continued exploration of the safety and efficacy of this non-hormonal selective neurokinin 3 receptor antagonist as a potentially novel therapy for vasomotor symptoms associated with menopause.

Added value of this study

This is a phase 3 randomised study assessing the use of a non-hormonal agent that targets the neurokinin 3 receptor to manage vasomotor symptoms associated with menopause. Women receiving fezolinetant 30 mg and 45 mg once daily had a reduced frequency and severity of vasomotor symptoms over a prolonged period that translated into a clinically meaningful improvement in quality of life, as measured by a menopause-specific patient-reported outcome tool. Although hormone therapy is the standard treatment for vasomotor symptoms, many women cannot take hormone therapy due to underlying medical conditions or medical history, or make a conscious choice not to take hormone therapy. This study highlights the efficacy and safety of fezolinetant in a diverse population that is representative of those women who might require non-hormonal therapy for vasomotor symptoms associated with menopause and who have limited treatment options.

Implications of all the available evidence

Results from this study add to the available data supporting the role of neurokinin 3 receptor antagonists in the treatment of vasomotor symptoms associated with menopause. The data indicate that fezolinetant 30 mg and 45 mg once daily were efficacious and well tolerated, supporting the potential use of fezolinetant as a first-in-class non-hormonal treatment option for women having vasomotor symptoms. Additional clinical studies to further define the safety and efficacy of fezolinetant are ongoing.

heat sensation and sweating that can cause cessation of usual activities.[3] Vasomotor symptoms can begin months to years before menopause (12 months after the last menstrual period), and persist for a median of 7·4 years.[4] However, a third of women continue to have moderate-to-severe vasomotor symptoms for more than 10 years.[2] Vasomotor symptoms can have a substantial negative impact on quality of life, contributing to physical and psychosocial impairment that can affect work performance, social activities, and personal and social relationships.[5] The negative association between vasomotor symptoms and health-related quality of life is strongest in women with frequent vasomotor symptoms,[6] and the discomfort associated with vasomotor symptoms can substantially affect sleep, leading to fatigue.[7,8] Vasomotor symptoms are also associated with anxiety and depressed mood,[7–9] and are independently associated with indicators of physical health risk in women, including cardiovascular disease, bone loss, and bone turnover.[10–12]

Menopausal hormone therapy with combined oestrogen and progestogen, or oestrogen alone, is effective for symptom management. However, many women cannot or choose not to take hormone therapy.[4,13] In a 2021 global cross-sectional survey of 3460 postmenopausal women with vasomotor symptoms associated with menopause, hormone therapy was contraindicated for about one in ten women (9% from USA, 12% from Europe, and 8% from Japan; absolute numbers of women are not available). Additionally, a high proportion of women indicated they were eligible for but did not want to use hormone therapy (54% from USA, 56% from Europe, and 79% from Japan; absolute numbers are not available).[13] Therefore, there is a need for safe, effective, targeted non-hormonal therapy for the relief of vasomotor symptoms associated with menopause, particularly for women who are unable or unwilling to take hormone therapy.

The thermoregulatory centre in the hypothalamus of the brain is innervated by kisspeptin–neurokinin B–dynorphin (KNDy) neurons. These neurons are stimulated by the neuropeptide neurokinin B, acting at the neurokinin 3 receptors, and inhibited by oestrogen. Declining and highly variable oestrogen concentrations during the menopausal transition alter neurokinin 3 receptor-mediated activation, resulting in hypertrophy of the KNDy neurons and dysregulation of the thermoregulatory centre. The thermoregulatory centre triggers heat dissipation effectors. Vasodilation in the skin causes heat loss, eliciting hot flashes, sweating, and chills.[14,15]

Fezolinetant is a selective neurokinin 3 receptor (NK3R) antagonist that blocks binding of neurokinin B to the KNDy neurons to restore normal sensitivity of the thermoregulatory centre in the hypothalamus. Results from phase 2 fezolinetant clinical studies showed a rapid and substantial reduction in frequency and severity of vasomotor symptoms, with improvements in health-related quality of life in women undergoing menopausal transition.[16–18] SKYLIGHT 1 (NCT04003155) and SKYLIGHT 2 (NCT04003142)[19] are 12-week randomised, placebo-controlled trials of fezolinetant 30 mg/day and 45 mg/day followed by a 40-week active treatment extension period and safety and efficacy analysis. In this study, we focus on the safety and efficacy outcomes from SKYLIGHT 1.

Methods

Study design and participants

SKYLIGHT 1 was a randomised, double-blind, placebo-controlled, phase 3 study in women aged 40–65 years having an average of seven or more moderate-to-severe hot flashes per day before randomisation and seeking treatment or relief for vasomotor symptoms. All women had spontaneous amenorrhoea for at least 12 consecutive months, spontaneous amenorrhoea for at least 6 months with biochemical criteria of menopause (follicle-stimulating hormone >40 IU/L), or bilateral oophorectomy for at least 6 weeks before the screening visit (with or without hysterectomy),[3] and a BMI of 18–38 kg/m². The key inclusion and exclusion criteria are presented in table 1. SKYLIGHT 1 was conducted at 97 facilities across the USA, Canada, Czech Republic, Hungary, Poland, Spain, and the UK. Demographic data (age, race, height, weight, and smoking status) were collected at screening. Sex was self-reported, and the inclusion criterion was born female.

SKYLIGHT 1 was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, and International Council for Harmonisation guidelines. An independent ethics committee or institutional review board reviewed the ethical, scientific, and medical appropriateness of the study at each site before data collection. Written informed consent was obtained before any study-related procedures were performed.

Inclusion criteria	Exclusion criteria
Born female, aged ≥40 years to ≤65 years at screening	Receiving strong or moderate cytochrome P450 1A2 inhibitors, hormone replacement therapy, hormonal contraceptive, or any treatment for vasomotor symptoms (prescription, over the counter, or herbal)
BMI ≥18 kg/m² to ≤38 kg/m²	Previous or existing history of a malignant tumour, except for basal cell carcinoma
Seeking treatment or relief for vasomotor symptoms associated with menopause and at screening having spontaneous amenorrhoea for ≥12 consecutive months; spontaneous amenorrhoea for ≥6 months with biochemical criteria of menopause (follicle-stimulating hormone >40 IU/L); or had bilateral oophorectomy ≥6 weeks before screening	Systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥80 mm Hg based on an average of two or three readings on at least two different occasions within the screening period; women who did not meet these criteria might, at the discretion of the investigator, be reassessed after initiation or review of antihypertensive measures; women with a medical history of hypertension could be enrolled at the discretion of the investigator once they were medically clear (stable and compliant)
Within 10 days before randomisation, women should have a minimum average of seven to eight moderate-to-severe hot flashes (vasomotor symptoms) per day, or 50–60 per week	History within the past 6 months of undiagnosed uterine bleeding
Normal, negative, or no clinically significant findings on mammogram within the previous 12 months or at screening	A medical condition or chronic disease (eg, history of neurological [eg, cognitive], hepatic, renal, cardiovascular, gastrointestinal, pulmonary [eg, moderate asthma], endocrine, or gynaecological disease) or malignancy that could confound interpretation of the study
Normal or not clinically significant Papanicolaou test result within the previous 12 months or at screening	Active liver disease, jaundice, or elevated liver aminotransferases (alanine aminotransferase or aspartate aminotransferase), elevated total or direct bilirubin, elevated international normalised ratio, or elevated alkaline phosphatase
Willing to undergo a transvaginal ultrasound to evaluate the uterus and ovaries at screening and at week 52 (end of treatment), and at early discontinuation for women who withdraw from the study before completion	Creatinine more than 1·5 times upper limit of normal; or estimated glomerular filtration rate ≤59 mL/min per 1·73 m² at screening
Willing to undergo an endometrial biopsy at screening and at week 52 (end of treatment) unless has had a supracervical or full hysterectomy; the endometrial biopsy obtained at screening should be considered evaluable and they should be willing to undergo endometrial biopsy in case of uterine bleeding or early discontinuation of the study or study drug	..

Table 1: **Key inclusion and exclusion criteria**

Randomisation and masking

Participants were randomised in a 1:1:1 ratio to placebo, fezolinetant 30 mg once daily, or fezolinetant 45 mg once daily for 12 weeks according to the randomisation schedule. The randomisation number was assigned using a web-based interactive response system (Cenduit, Nottingham, UK) and used to stratify participants by smoking status (active smoker or non-smoker). The investigators, project team members, clinical staff, and participants were masked to treatment assignment. Participants took two tablets orally per day with the placebo and active tablets being indistinguishable in appearance and shape. Masking was managed and monitored by the interactive response technology and was not compromised during the study.

See Online for appendix

Procedures

Participants took their assigned study drug orally once per day. The schedule of assessments and visits is shown in the appendix (p 3). Participants who completed the 12-week placebo-controlled period could enter a 40-week active treatment extension period. Women treated with fezolinetant continued to receive their randomised dose whereas women in the placebo group were rerandomised to fezolinetant 30 mg or 45 mg. Participants and investigators were masked to the dose during the extension phase (appendix p 3).

Outcomes

The primary objective of SKYLIGHT 1 was to evaluate the efficacy of fezolinetant versus placebo on the frequency and severity of moderate-to-severe vasomotor symptoms. The four coprimary endpoints were mean change in frequency of moderate-to-severe vasomotor symptoms from baseline to weeks 4 and 12, and mean change in severity of moderate-to-severe vasomotor symptoms from baseline to weeks 4 and 12. Data on vasomotor symptoms were collected using an electronic hot flashes diary, completed daily by the study participants from screening to the follow-up visit. The hot flashes diary was an interactive, electronic data-capture system available for data entry 24 h/day. Women were provided with a reference guide within the diary, which included definitions as follows:[3] mild symptoms (ie, sensation of heat without sweating); moderate symptoms (ie, sensation of heat with sweating, able to continue activity); and severe symptoms (ie, sensation of heat with sweating, causing cessation of activity).

The key secondary endpoint was mean change in the total score in Patient-Reported Outcomes Measurement Information System Sleep Disturbance—Short Form 8b (PROMIS SD SF 8b) from baseline to week 12. The PROMIS SD SF 8b assesses self-reported sleep disturbance in the previous 7 days and includes perceptions of restless sleep, satisfaction with sleep, refreshing sleep, difficulties sleeping, difficulties getting to sleep or staying asleep, amount of sleep, and sleep quality. Responses to each of the eight items range from 1 to 5; the range of possible summed raw scores is 8 to 40, with higher scores indicating more disturbed sleep. Participants completed the PROMIS SD SF 8b electronically via a tablet at the study site visit (every 4 weeks) without assistance. Other secondary endpoints included the mean change in frequency and severity of moderate-to-severe vasomotor symptoms from baseline to each week up to week 12 and percentage reductions of at least 50% and at least 75% in the frequency of moderate-to-severe vasomotor symptoms from baseline to each week up to week 12.

The pre-specified exploratory endpoints were Patient Global Impression of Change in Sleep Disturbance (PGI-C SD), mean change from baseline on Patient Global Impression of Severity in Sleep Disturbance (PGI-S SD), and mean change in total and domain scores of Menopause-Specific Quality of Life (MENQOL). The patient-reported outcome measure of PGI-C SD asked participants to rate how well they were sleeping at that timepoint compared with the start of the study using a scale ranging from 1 (much better) to 7 (much worse). PGI-S SD asked participants to rate the severity of any present problems while sleeping at night using a scale ranging from 1 (no problems) to 4 (severe problems). MENQOL is a 29-item patient-reported outcome measure assessing the effect of four domains of menopausal symptoms in the past week: vasomotor, psychosocial, physical, and sexual. Specific symptoms are rated as present or not present, and if present they are rated on a scale of 0 (not bothersome) to 6 (extremely bothersome). The MENQOL Total Score is the mean of the four domain scores.

Safety was assessed using the frequency of treatment-emergent adverse events (adverse event observed after first administration of the drug and 21 days after the last dose) throughout the study. Treatment-emergent adverse events were coded using the Medical Dictionary for Regulatory Activities (version 23.0) and were summarised by the system organ class and preferred term. Clinical laboratory tests were done at screening and all visits and included haematology and biochemistry, such as liver safety assessments. Endometrial biopsy was performed if there was any uterine bleeding, on early study discontinuation, and at the end of the extension period.

Statistical analysis

The planned sample size was 450 women (150 in each treatment group). Details of how the target sample size was determined are presented in the appendix (p 2). Continuous data were summarised with descriptive statistics (number of participants, mean, standard deviation, minimum, median, and maximum), and frequency and percentage for categorical data. The efficacy analyses used the full analysis set comprising all randomly assigned participants who received at least one dose of study drug. A sensitivity analysis was done for the coprimary efficacy endpoints on the per protocol set (excluding participants with no measurement of the primary efficacy endpoint at weeks 4 or 12, <85% interactive diary compliance, and <85% treatment compliance). The safety analysis set also consisted of all randomly assigned participants who took at least one dose of study drug. If a participant received a different treatment in error, they were included with randomly assigned participants for the full analysis set, but with the treatment group based on first dose for the safety analysis set.

All statistical comparisons were conducted using two-sided tests at the $\alpha=0\cdot05$ significance level. For each of the four coprimary efficacy endpoints, a mixed model for repeated measures was used with treatment group, week, and smoking status (current *vs* former or never) as factors,

and baseline weight and baseline measurement as covariates, as well as an interaction of treatment by week and of baseline measurement by week. The family-wise type I error rate for comparing the two fezolinetant dose groups with placebo for the four coprimary efficacy endpoints was controlled using a Hochberg approach. All four coprimary endpoints had to be significant for a given dose to be considered successful, and the largest p value in each dose group was used because it represented the least significant of the coprimary endpoints. If all coprimary endpoints were significant (fezolinetant at both doses *vs* placebo), the 5% α value from the coprimary endpoint analyses passed to testing the key secondary endpoint as part of the family-wise error rate. An unstructured covariance structure shared across treatment groups was used to model the within-patient errors. The Kenward-Roger approximation was used to estimate the maximum likelihood-based repeated measures approach. The treatment difference was estimated at all study weeks.

The mixed model repeated measures used all available on-treatment data to inform mean treatment effect estimates without requiring explicit imputation for missing data (ie, discontinued participants). This approach is consistent with the hypothetical strategy used for the estimand, which is to compare participants as though they had continued the assigned treatment. Generally, the mechanism of missing data was assumed to be missing at random. There was no explicit imputation of missing data for the primary analysis. To evaluate the robustness of the primary analysis results versus departure from the underlying missing-at-random assumption, a sensitivity analysis was conducted using a discontinuation-reason-based multiple imputation method. Specifically, a jump-to-reference (ie, placebo) method was used to impute the missing data from participants who discontinued active treatment due to treatment-emergent adverse events by assuming that the treatment benefits are diminished after discontinuation of the treatment.

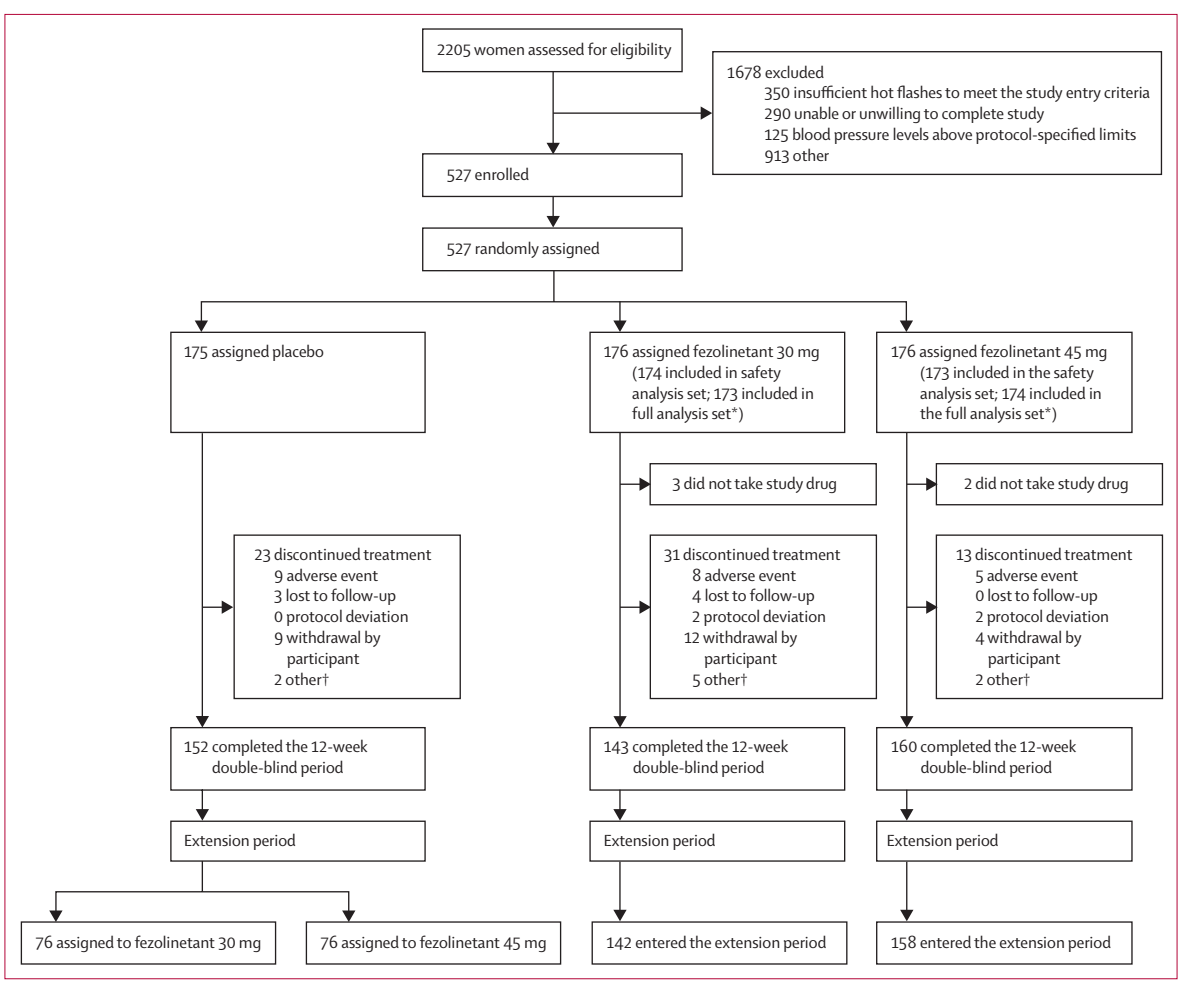

Figure 1: **Trial profile**

*One participant who was randomly assigned to fezolinetant 45 mg received fezolinetant 30 mg in error; they were included in the fezolinetant 45 mg group for the primary efficacy analysis, and the fezolinetant 30 mg for the safety analysis. †For example, non-compliance with the study, relocation, inability to follow study protocols due to the COVID-19 pandemic, and not meeting study criteria.

Comparisons between the fezolinetant and placebo groups were calculated on the basis of least-squares means. The daily mean frequency and severity per week (eg, weeks 4 and 12) were calculated as the average frequency and severity over non-missing days from 7 days. Participants had to provide data for 50% of any given week (≥4 days) for their data to be included in the analysis. The key secondary endpoint (PROMIS SD SF 8b) and MENQOL total and domain scores were analysed using mixed model repeated measures, similar to the analysis of the coprimary endpoints with spatial power as the back-up covariance structure. The PGI-C SD and PGI-S SD were analysed using the Cochran-Mantel-Haenszel test with modified ridit scores (SAS version 9.4). This study is registered with ClinicalTrials.gov, number NCT04003155.

	Placebo (n=175)	Fezolinetant 30 mg (n=174)	Fezolinetant 45 mg (n=173)	Total (n=522)
Ethnicity				
Not Hispanic or Latina	128 (74%)	131 (75%)	126 (73%)	385 (74%)
Hispanic or Latina	46 (26%)	43 (25%)	47 (27%)	136 (26%)
Missing	1 (1%)	0	0	1 (<1%)
Race				
Black or African American	28 (16%)	21 (12%)	26 (15%)	75 (14%)
White	142 (81%)	148 (86%)	141 (82%)	431 (83%)
Other*	5 (3%)	4 (2%)	6 (3%)	15 (3%)
Missing	0	1 (1%)	0	1 (<1%)
Age, years	54·7 (4·8); 41–65	54·2 (4·9); 42–65	54·2 (5·1); 40–65	54·4 (4·9); 40–65
Weight, kg	74·41 (12·14); 47·7–111·0	75·24 (14·07); 42·0–121·2	75·50 (12·66); 50·6–110·6	75·05 (12·97); 42·0–121·2
BMI, kg/m²	28·19 (4·28); 18·8–37·7	28·14 (4·83); 18·0–37·8	28·28 (4·35); 18·4–37·9†	28·20 (4·49); 18·0–37·9†
Smoking status‡				
Current	22 (13%)	22 (13%)	22 (13%)	66 (13%)
Former or never	153 (87%)	152 (87%)	151 (87%)	456 (87%)
Time since onset of hot flashes, months	81·9 (73·6)	77·4 (66·3)	71·9 (59·3)	77·1 (66·7)
Amenorrhoea				
No§	5 (3%)	4 (2%)	2 (1%)	11 (2%)
Yes	170 (97%)	170 (98%)	171 (99%)	511 (98%)
Hysterectomy				
No	124 (71%)	113 (65%)	117 (68%)	354 (68%)
Yes	51 (29%)	61 (35%)	56 (32%)	168 (32%)
Oophorectomy				
No	137 (78%)	137 (79%)	136 (79%)	410 (79%)
Yes	38 (22%)	37 (21%)	37 (21%)	112 (22%)
Previously used hormone therapy for hot flashes or night sweats				
No	137 (81%)	141 (82%)	138 (82%)	416 (82%)
Yes	33 (19%)	31 (18%)	30 (18%)	94 (18%)
Missing	5 (3%)	2 (1%)	5 (3%)	12 (2%)

Data are n (%), mean (SD); range, or mean (SD). Age range was defined as whole numbers. *American Indian or Alaska Native, Asian, Pacific Islander, or more than one race. †One participant missing. ‡Stratification factor. §Participants had surgical amenorrhoea (hysterectomy with or without oophorectomy [unilateral or bilateral]).

Table 2: **Key participant demographics and baseline characteristics (safety analysis set)**

Role of the funding source

The funder of the study was Astellas Pharma. Employees of Astellas (FDO, ML, CF, and ME) made substantial contributions to conception or design of the study, and the acquisition, analysis, and interpretation of the data for the study; drafted the manuscript and revised the manuscript critically for important intellectual content; provided final approval of the manuscript version to be published; and agree to be accountable for all aspects of the work.

Results

Between July 11, 2019, and Aug 11, 2021, 2205 women were recruited and 527 were randomly assigned to treatment groups. 522 women had at least one dose of study drug and were included in the safety analysis set (175 in the placebo group, 174 in the fezolinetant 30 mg group, 173 in the fezolinetant 45 mg group; figure 1). One participant was randomly assigned to fezolinetant 45 mg but in error received fezolinetant 30 mg, meaning that the full analysis set consisted of 175 participants in the placebo group, 173 in the fezolinetant 30 mg group, and 174 in the fezolinetant 45 mg group.

All treatment groups were similar with respect to demographic and baseline characteristics (table 2). The proportion of women self-identifying as Black or African American ranged from 21 (12%) of 173 participants with available data in the fezolinetant 30 mg group to 28 (16%) of 175 in the placebo group, which is reflective of North American and European populations.

Both fezolinetant doses significantly reduced the frequency and severity of moderate-to-severe vasomotor symptoms per 24 h at weeks 4 and 12 compared with placebo (figure 2A, B). These results were mirrored in the per protocol set (appendix p 6).

In the 173 women assigned to fezolinetant 30 mg, the mean frequency of daily moderate-to-severe vasomotor symptoms (events) reduced from 10·7 events per 24 h (SD 4·7) at baseline to 5·4 events per 24 h (3·8) at week 4 and 4·5 events per 24 h (3·7) at week 12 (mean percentage change from baseline –48% [SD 35·0] at week 4, –56% [35·9] at week 12). In the 174 women assigned to fezolinetant 45 mg, the mean frequency of daily moderate-to-severe vasomotor symptoms reduced from 10·4 events per 24 h (3·9) at baseline to 5·2 events per 24 h (4·5) at week 4 and 4·1 events per 24 h (3·9) at week 12 (mean percentage change –51% [35·4] at week 4, –61% [32·7] at week 12). By comparison, in the 175 women assigned to placebo, the mean frequency of daily moderate-to-severe vasomotor symptoms reduced from 10·5 events per 24 h (3·8) at baseline to 7·3 events per 24 h (4·3) at week 4 and 6·9 events per 24 h (4·7) at week 12 (mean percentage change –30% [35·3] at week 4, –35% [39·7] at week 12).

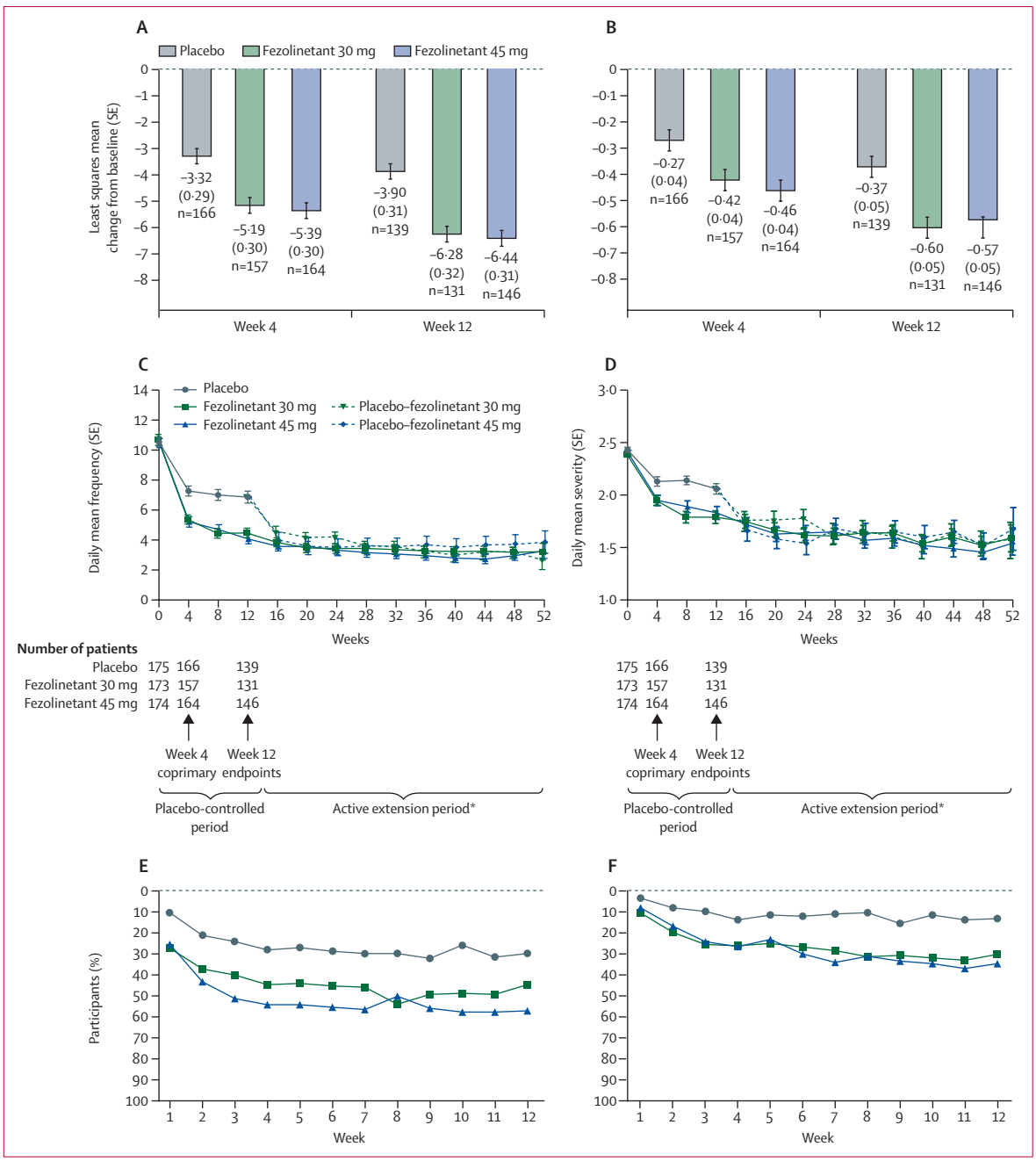

Figure 2: **Change from baseline in frequency and severity of moderate-to-severe vasomotor symptoms**
Coprimary outcomes of least squares mean change from baseline in frequency of moderate-to-severe vasomotor symptoms (A) and severity (B) per 24 h at weeks 4 and 12 in the full analysis set (not everyone in the full analysis set had vasomotor symptom data available at all timepoints leading to missing data; the missing data are handled using a mixed model for repeated measures without specific imputation in the analysis). Outcomes from the extension period showing changes in frequency (C) and severity (D) of moderate-to-severe vasomotor symptoms over the 52-week treatment in the full analysis set with at least one dose of fezolinetant and in full analysis set–fezolinetant exposure (ie, the two fezolinetant groups that continued treatment and the placebo group that was rerandomised to fezolinetant 30 mg or 45 mg). Proportions of participants with at least a 50% (E) and at least a 75% (F) reduction in frequency of moderate-to-severe vasomotor symptoms per 24 h by week in the full analysis set. *Women previously taking placebo randomly assigned to fezolinetant 30 mg or 45 mg.

For frequency of moderate-to-severe vasomotor symptoms, compared with placebo, the change in least squares means for fezolinetant 30 mg was −1·87 (SE 0·42; p<0·001) and −2·07 (0·42; p<0·001) for fezolinetant 45 mg at week 4. At week 12, the difference in the change in least squares mean compared with placebo was −2·39 (0·44; p<0·001) for fezolinetant 30 mg and −2·55 (0·43; p<0·001) for fezolinetant 45 mg. For severity of moderate-to-severe vasomotor symptoms, the difference in the change in least squares mean

compared with placebo was –0·15 (0·06; p=0·012) for fezolinetant 30 mg and –0·19 (0·06; p=0·002) for fezolinetant 45 mg at week 4, and –0·24 (0·08; p=0·002) for 30 mg and –0·20 (0·08; p=0·007) for fezolinetant 45 mg at week 12 (figure 2). Improvement in the frequency and severity of moderate-to-severe vasomotor symptoms was observed as early as 1 week after treatment onset (unadjusted p<0·001 for frequency and p=0·006 for severity for both fezolinetant doses *vs* placebo) and was maintained throughout the 12-week placebo-controlled period (figure 2; appendix p 5).

For the key secondary endpoint, the observed improvements in patient-reported sleep disturbance for fezolinetant 30 mg and 45 mg versus placebo were not significant at week 12 (appendix p 7). Exploratory analyses of sleep showed more participants in both fezolinetant groups reported a positive change in PGI-C SD than participants in the placebo group, at weeks 4 and 12. Fewer participants reported severe problems with sleep disturbance in the fezolinetant 45 mg group than in the placebo group, at weeks 4 and 12 (figure 3; appendix p 8).

The percentages of participants achieving at least 50% and at least 75% reductions in frequency of moderate-to-severe vasomotor symptoms are shown in figure 2. By week 12 the frequency of vasomotor symptoms had reduced by at least 50% in 77 (45%) of 173 participants in the fezolinetant 30 mg group and 99 (57%) of 174 in the fezolinetant 45 mg group, versus 52 (30%) of 175 in the placebo group. MENQOL total score and the vasomotor domain significantly improved from baseline to weeks 4 and 12 in participants treated with fezolinetant 30 mg and 45 mg versus placebo (p≤0·002; appendix p 9).

Over 12 weeks, treatment-emergent adverse events were reported by 65 (37%) of 174 women in the fezolinetant 30 mg group, 75 (43%) of 173 in the fezolinetant 45 mg group, and 78 (45%) of 175 in the placebo group (table 3). Headache was the most common treatment-emergent adverse event and was reported by nine (5%) women receiving fezolinetant 30 mg, 11 (6%) receiving fezolinetant 45 mg, and 13 (7%) receiving placebo. Serious treatment-emergent adverse events occurred infrequently, with a total of five reported. These events were increased liver function test (n=1) and transaminases (n=1) in the fezolinetant 30 mg group; paraesthesia (n=1) and varicose vein (n=1) in the fezolinetant 45 mg group; and cholelithiasis (n=1) in the placebo group. The only serious, drug-related, treatment-emergent adverse events occurred in the fezolinetant 30 mg group: increased transaminases and liver function test, as reported by the investigator.

The incidence of liver enzyme elevations was low. In general, increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) were asymptomatic; isolated, intermittent, or transient; and resolved during treatment or, for two participants, after treatment discontinuation. There were no reported Hy's law cases in any of the groups (ALT or AST more than three times the upper limit of normal [ULN] and bilirubin more than two times the ULN with no other reason to explain the combination).[20] The liver safety assessments showed that

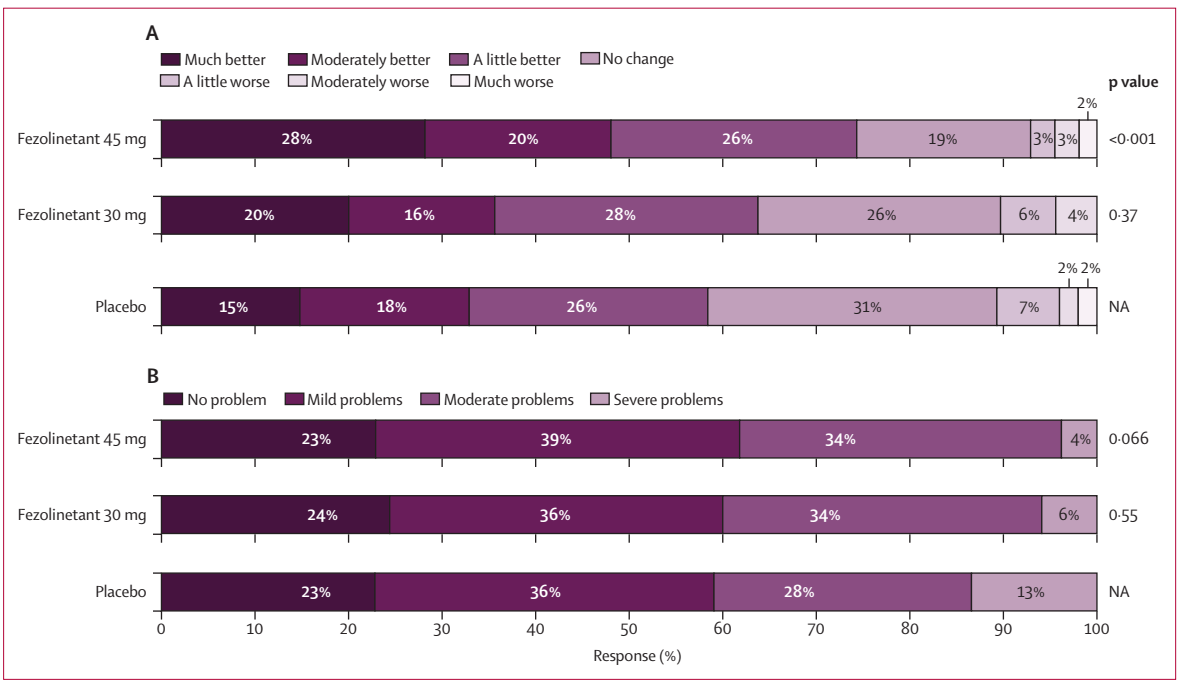

Figure 3: **Change from baseline in the Distribution of Patient Global Impression of Change in Sleep Disturbance at week 12 (A) and Patient Global Impression of Severity in Sleep Disturbance (B) at week 12 (full analysis set)**
NA=not applicable.

	Placebo (n=175)	Fezolinetant 30 mg (n=174)	Fezolinetant 45 mg (n=173)
Any TEAE	78 (45%)	65 (37%)	75 (43%)
Drug-related TEAEs	22 (13%)	17 (10%)	13 (8%)
Serious TEAEs	1 (1%)	2 (1%)	2 (1%)
Drug-related serious TEAEs	0	2 (1%)*	0
TEAEs causing permanent discontinuation of study drug	9 (5%)†	10 (6%)‡	4 (2%)§
Drug-related TEAEs causing permanent discontinuation of study drug	7 (4%)	6 (3%)	3 (2%)
Deaths	0	0	0
TEAEs by preferred term (≥2% for any group)			
Headache	13 (7%)	9 (5%)	11 (6%)
Blood glucose increased	0	6 (3%)	6 (3%)
Abdominal pain upper	2 (1%)	2 (1%)	4 (2%)
Arthralgia	1 (1%)	4 (2%)	2 (1%)
Blood creatinine phosphokinase increased	0	2 (1%)	4 (2%)
Nasopharyngitis	2 (1%)	4 (2%)	1 (1%)
ALT increased	4 (2%)	1 (1%)	3 (2%)
γ-glutamyltransferase increased	4 (2%)	1 (1%)	2 (1%)
Nausea	4 (2%)	0	2 (1%)
Migraine	4 (2%)	0	1 (1%)
TEAEs of special interest¶			
Liver test elevations	5 (3%)	6 (3%)	7 (4%)
Depression	2 (1%)	2 (1%)	3 (2%)
Uterine bleeding	2 (1%)	3 (2%)	2 (1%)
Bone fractures	0	1 (1%)	1 (1%)
Effect on memory	0	1 (1%)	0
Thrombocytopenia	1 (1%)	0	1 (1%)
Wakefulness	1 (1%)	0	1 (1%)
Endometrial hyperplasia, cancer, or disordered proliferative endometrium	0	0	0
Potential abuse liability	0	0	0
Liver safety assessments			
ALT >3 times ULN	1/173 (1%)	2/163 (1%)	0/170
AST >3 times ULN	0/173	2/163 (1%)	0/170
ALT or AST >3 times ULN‖	1/173 (1%)	2/163 (1%)	0/170
ALP >1·5 times ULN	3/173 (2%)	3/163 (2%)	1/170 (1%)
ALT or AST >3 times ULN and bilirubin >2 times ULN‖	0	0	0

Data are n (%) or n/N (%). Data are for the safety analysis set (randomised patients who took ≥1 dose of study drug). Two participants had confirmed and suspected cases of COVID-19 (one receiving fezolinetant 30 mg and one receiving fezolinetant 45 mg). For the liver safety assessments, the denominator is the number of participants who had at least one non-missing value during the 12-week double-blind treatment. ALP=alkaline phosphatase. ALT=alanine aminotransferase. AST=aspartate aminotransferase. ULN=upper limit of normal. *Transaminases increased and liver function test increased. †Dry mouth, glossodynia, and paraesthesia oral (n=1); dyspepsia and nausea (n=1); nausea, dizziness, headache, migraine, and skin discolouration (n=1); headache (n=2); nausea and abdominal pain upper (n=1); ALT increased (n=1); weight increased (n=1); and diarrhoea and abdominal pain upper (n=1). ‡Dizziness (n=1); myalgia (n=1); fungal infection (n=1); transaminases increased (n=1); endometrial disorder (n=1); dizziness and hepatic pain (n=1); diverticulitis (n=1); aggression, muscle twitching, and palpitations (n=1); upper abdominal pain (n=1); and liver function test increased (n=1). §A mass in the distal femur (n=1); dizziness and headache (n=1); abdominal pain upper (n=2). ¶Standardised Medical Dictionary for Regulatory Activities Queries (SMQ) were used for searching for thrombocytopenia (SMQ broad; haematopoietic thrombocytopenia), liver test elevations (SMQ broad; liver-related investigations, signs, and symptoms), abuse liability (SMQ narrow; drug abuse, dependence, and withdrawal), and depression (SMQ broad; depression, excluding suicide and self-injury). To further complement these searches, relevant high-level terms and preferred terms were used in the search strategy for the abuse liability and depression TEAEs of special interest. ‖Combination of values measured within the same day or within 1 day apart.

Table 3: **Overview of treatment-emergent adverse events (TEAEs) during the 12-week double-blind period (safety analysis set)**

one participant in the placebo group, two in the fezolinetant 30 mg group, and none in the fezolinetant 45 mg group had ALT or AST results greater than three times the ULN (table 3). None of the women in the placebo or fezolinetant 45 mg groups had ALT or AST results greater than five times the ULN. Two women from the fezolinetant 30 mg group had ALT or AST greater than five times the ULN, one of whom had an ALT or AST result greater than 20 times the ULN. This participant began treatment with ketorolac trometamol (two intramuscular injections and oral), morphine (one intramuscular injection), hydrocodone and paracetamol, clonazepam, and gabapentin for mild knee pain 4 days before the treatment-emergent adverse event of increased liver function test. The other participant had an ALT result greater than five times the ULN and was taking oxycodone hydrochloride and paracetamol for rheumatoid arthritis pain.

An increase in blood glucose concentration was observed in six (3%) of 174 women assigned to fezolinetant 30 mg and six (3%) of 173 women assigned to fezolinetant 45 mg (table 3). However, the mean blood glucose reduced from baseline at week 12 in the fezolinetant groups (placebo 0·25 mmol/L [SD 1·45] *vs* fezolinetant 30 mg –0·05 mmol/L [1·46] *vs* fezolinetant 45 mg –0·02 mmol/L [1·33]).

In the 40-week active treatment extension period, 76 women were randomly assigned from placebo to fezolinetant 30 mg, and 76 were randomly assigned from placebo to fezolinetant 45 mg (figure 1). Baseline demographics for these groups are shown in the appendix (p 11). Fezolinetant efficacy persisted during the study as

shown by the change in the frequency and severity of vasomotor symptoms over time (figure 2) and change in sleep disturbance at weeks 24 and 52 (appendix p 12).

Over 52 weeks of study, 48 (63%) of 76 participants in the placebo–fezolinetant 30 mg group, 37 (49%) of 76 in the placebo–fezolinetant 45 mg group, 108 (62%) of 174 in the fezolinetant 30 mg group, and 115 (66%) of 173 in the fezolinetant 45 mg group had at least one treatment-emergent adverse event (appendix p 13). The incidence of treatment-emergent adverse events by preferred term was balanced across the placebo–fezolinetant 30 mg and 45 mg groups and fezolinetant 30 mg and 45 mg groups (appendix p 13). The most commonly reported treatment-emergent adverse events were headache and COVID-19. Liver safety assessments showed that nine participants had ALT or AST concentrations greater than three times the ULN (n=4 fezolinetant 30 mg, n=4 fezolinetant 45 mg, n=1 placebo–fezolinetant 30 mg, n=0 placebo–fezolinetant 45 mg), and there were no Hy's law cases (appendix p 14).

Discussion

In this phase 3, randomised controlled trial, four coprimary efficacy endpoints were met. Fezolinetant 30 mg and 45 mg once daily significantly improved the frequency and severity of vasomotor symptoms at week 4. Fezolinetant efficacy was observed as early as week 1, with continued improvement to week 4 and a sustained benefit throughout the 12-week double-blind period. At week 12, least squares mean reduction in the frequency of vasomotor symptoms was greater than 50% in both fezolinetant groups, and a 50% reduction in symptoms has been reported in the literature to be clinically significant.[21] Importantly, persistence of efficacy was observed over 52 weeks of treatment.

The significant reduction in the frequency and severity of vasomotor symptoms over 12 weeks translated to a clinically meaningful improvement in quality of life as measured by the MENQOL, a menopause-specific patient-reported outcome tool. The observed improvement in MENQOL total score suggests that each fezolinetant dose substantially improved quality of life from as early as week 4 of the study. The identically designed SKYLIGHT 1 and SKYLIGHT 2 studies provide data on fezolinetant efficacy in more than 1000 women.

Although sleep disturbance improved, as measured by the PROMIS SD SF 8b, this change was not significant in either fezolinetant groups at 12 weeks. However, significance was achieved with fezolinetant 45 mg at weeks 4 and 12 in SKYLIGHT 2.[19] Of note, disturbed sleep was not a prerequisite for study inclusion, which could affect these results. As this study primarily assessed vasomotor symptoms, further investigation of the effect of fezolinetant on sleep in specifically designed trials is required to fully understand any effect. However, several sleep-related, patient-reported outcome measures were used in the study. These data show, at weeks 4 and 12, more participants reported a positive change in PGI-C SD and fewer participants had severe sleep problems with fezolinetant than placebo.

Up to 80% of women undergoing menopausal transition have vasomotor symptoms.[1,5] Non-hormonal options for women who cannot take or choose not to take hormone thereapy[22] are scarce, with only low-dose paroxetine approved by the US Food and Drug Administration for vasomotor symptoms.[23] Additionally, many selective serotonin reuptake inhibitors are metabolised by CYP2C19 and CYP2D6 enzymes. These drugs might be less effective in populations with a higher prevalence of particular polymorphisms in the *CYP2C19* and *CYP2D6* genes, such as the Black population.[24,25] Alternative non-hormonal treatments include off-label use of clonidine, gabapentin, other selective serotonin reuptake inhibitors, and serotonin–norepinephrine reuptake inhibitors, and herbal medicines (ie, black cohosh, ginseng, gingko biloba, St John's wort, and dong quai). However, these agents have either modest efficacy with some tolerability concerns, or there is conflicting evidence regarding efficacy.[26]

Five neurokinin receptor antagonists have been investigated for vasomotor symptoms: elinzanetant (NT-814), pavinetant, SJX-653, MLE-301, and fezolinetant. Fezolinetant is more than 450-fold more selective for human NK3R compared with NK1 and NK2 receptor antagonists.[14] Elinzanetant (NT-814), a non-selective NK1R and NK3R antagonist with greater potency at the NK1 receptor, is in phase 3 trials.[27] Pavinetant (MLE4901), a potential NK3R antagonist,[28] was discontinued for further development after an assessment of risks and benefits. Observed hepatic adverse events were proposed to be idiosyncratic and related to the chemical structure of pavinetant rather than a general class effect for NK3R antagonists.[29] Development of SJX-653 and MLE-301 (NK3R antagonists) was also discontinued following phase 2 and 1 clinical trials, respectively. Hepatic safety of NK3R antagonists was highlighted for appropriate monitoring. In response, the fezolinetant clinical programme was designed in conjunction with feedback from regulatory authorities to comprehensively monitor liver function, and the current study included a liver safety monitoring board.

Over the 12-week double-blind period of this study, the incidence of individual treatment-emergent adverse events and liver enzyme elevations were low, and few serious treatment-emergent adverse events occurred. Long-term, placebo-controlled safety data will be available from the SKYLIGHT 4 study (NCT04003389). Two women had drug-related, serious treatment-emergent adverse events (transaminase increased and liver function tests increased) that met protocol-specified criteria for treatment discontinuation and resolved on discontinuation of fezolinetant. Furthermore, the frequency of treatment-emergent adverse events leading to treatment withdrawal was low, and the safety profile of both fezolinetant doses

was unremarkable. No clinically relevant changes in haematology, biochemistry, coagulation, or urinalysis parameters occurred across treatment groups. Three participants had elevations in ALT or AST concentrations greater than three times the ULN in the 12-week randomised period, but these elevations were generally asymptomatic; isolated, intermittent, or transient; and resolved during treatment or after treatment discontinuation. Increased blood glucose concentrations were observed in some participants in the fezolinetant group, but most cases were minimally elevated above ULN and independent of a medical history of diabetes. Furthermore, the overall change from baseline to week 12 indicated a reduction in blood glucose concentrations in the fezolinetant groups. There was no requirement to measure glucose concentration after fasting or at consistent collection times throughout the day, making interpretation of these results challenging. Regarding treatment-emergent adverse events of special interest, the incidence was similar across the three treatment groups, with no evidence of dose dependency.

Although favourable, few conclusions can be drawn from the 12-week short-term safety data. Data from the 52 weeks of study, although not placebo-controlled after 12 weeks, affirm the safety findings and the overall safety data in SKYLIGHT 1 were similar to those observed in SKYLIGHT 2.[19]

In this study, the frequency and severity of vasomotor symptoms reduced in the placebo group indicating a placebo effect. A strong placebo effect is widely reported in studies investigating potential treatments for vasomotor symptoms.[30] SKYLIGHT 1 was designed to conform to the US Food and Drug Administration Draft Guidance on clinical studies of vasomotor symptoms, with a placebo group and requirement for four coprimary endpoints.[3] Despite the placebo effect, significant differences were found for both fezolinetant doses versus placebo at weeks 4 and 12.

Further studies investigating other menopausal symptoms (eg, mood and sexual wellbeing) could provide a more comprehensive overview of treatment benefit. This study was not designed to compare active doses. NK3R antagonists offer a novel approach for the management of vasomotor symptoms. Many women are unable or unwilling to take hormone therapy and have few effective non-hormonal treatment options available. Results from SKYLIGHT 1 show that fezolinetant 30 mg and 45 mg once daily were efficacious for long-term treatment of moderate-to-severe vasomotor symptoms associated with menopause. Vasomotor symptoms significantly improved by the first week of treatment, were maintained to week 12, and persisted throughout 52 weeks, without evidence of tachyphylaxis. NK3R antagonists have the potential to provide alternative non-hormonal treatment options to address the unmet need for many women who have vasomotor symptoms.

Contributors

SL was the coordinating investigator for the study and NS, RCT, GN-P, PS, MS, and AC were scientific steering committee members. SL, FDO, ML, CF, and ME were responsible for the acquisition of study data and FDO, ML, and ME verified the data. FDO, ML, CF, and ME contributed to the concept and design of the study. ML was responsible for the statistical analyses. All authors had full access to the study data, were involved in the analysis and interpretation of the data, take responsibility for the accuracy of the analysis, and had authority over manuscript preparation and the decision to submit the manuscript for publication. All authors approved the manuscript for submission.

Declaration of interests

SL has received honoraria from AbbVie and research funding from AbbVie, Amgen, Aspira, Estetra, and Janssen. NS is a study investigator, member of the Scientific Advisory Board, and consultant for Astellas, a member of the Scientific Advisory Board for Amazon (Project Ember), Menogenix, and Que Oncology, a consultant for Ansh Labs, on the Program Committee for the North American Menopause Society (NAMS), past President of the Society for Reproductive Investigation, and is on the Nominating Committee for the Endocrine Society. RCT is a consultant and adviser for Astellas, a consultant for Bayer Healthcare, Happify Health, Pfizer, Procter and Gamble, and Vira Health, and is on the Board of Directors for NAMS. GN-P is a member of the Scientific Advisory Board for Astellas and Ferring Pharmaceuticals, has research funding from Merck, is Vice President of Diversity, Equity and Structural Change for the Society for Gynecological Investigations, and holds Committee Membership of the Endocrine Society. PS is a consultant for Astellas, board member for the European Menopause and Andropause Society (EMAS) and Deutsche Menopause Gesellschaft (DMG), and President of the Swiss Society for Gynecological Endocrinology and Menopause (SGEM). MS is on the advisory board or receives consulting fees or honoraria from Aspen, Astellas, BioSyent, Bayer, Duchesnay, GlaxoSmithKline, Merck, Mithra, Pfizer, Searchlight, Sprout, Sunovion, and Therapeutics MD, and fulfils a leadership or fiduciary role for the International Menopause Society, Terry Fox Research Institute, and Research Canada. AC is past President of the European Menopause and Andropause Society, and a consultant for Astellas, Theramex, and ItalFarmaco. FDO, ML, CF, and ME are employees of Astellas Pharma.

Data sharing

On request, and subject to specific criteria, conditions, and exceptions, Astellas will provide access to anonymised patient-level data from completed, Astellas-sponsored, phase 1 to 4 interventional clinical studies conducted for products and indications that have been approved in any country, and for terminated compounds. Approval must have been granted by the agencies of the main regions USA, EU, and Japan. If approval is sought in one or two regions, approval must have been granted by those agencies. Where available, the following anonymised patient-level data and information is provided for each clinical study: raw dataset, analysis ready dataset, protocols with any amendments or addenda, annotated case report form, statistical analysis plan, dataset specifications, and clinical study report. Additionally, data may be available on request. Researchers can request access at https://www.clinicalstudydatarequest.com. For the Astellas criteria on data sharing see: https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx.

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