Efficacy and safety of fezolinetant for moderate-severe vasomotor symptoms associated with menopause in individuals unsuitable for hormone therapy: phase 3b randomised controlled trial

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ABSTRACT

OBJECTIVES

To assess the efficacy and safety of the non-hormonal, neurokinin 3 receptor antagonist, fezolinetant, to treat moderate-severe vasomotor symptoms associated with menopause in individuals unsuitable for hormone therapy.

DESIGN

Phase 3b randomised controlled trial.

SETTING

16 countries.

PARTICIPANTS

453 individuals aged 40-65 years with moderate-severe vasomotor symptoms associated with menopause who were considered unsuitable candidates for hormone therapy (contraindicated, caution (based on medical history), stoppers (previous discontinuation of hormone therapy), or averse (informed choice not to use hormone therapy)) were randomised to receive fezolinetant (n=227) or placebo (n=226).

INTERVENTION

Fezolinetant 45 mg or placebo once daily for 24 weeks.

MAIN OUTCOME MEASURES

The primary endpoint was mean change in daily frequency of moderate-severe vasomotor symptoms from baseline to week 24. Secondary endpoints were mean change in symptom severity, sleep disturbance using the Patient-Reported Outcome Measurement Information System Sleep Disturbance Short Form (PROMIS SD-SF) 8b total score, and safety.

RESULTS

370 (81.7%) participants completed the study (fezolinetant=195, placebo group=175). The safety and full analysis sets comprised 452 participants who received at least one dose of study drug. Mean age was 54.5 (standard deviation 4.7) years and most of the participants (435 (96.7%) were white and categorised as either hormone therapy averse (168 (37.2%)) or caution (165 (36.5%)). At week 24, fezolinetant significantly reduced the frequency (least squares mean difference −1.93, 95% confidence interval (CI) −2.64 to −1.22; P<0.001) and severity of vasomotor symptoms (−0.39, −0.57 to −0.21; P<0.001). At week 24, the fezolinetant group had a greater reduction in sleep disturbance (PROMIS SD-SF 8b total score) compared with placebo (−2.5, −3.9 to −1.1; P<0.001). Improvements over placebo were observed as early as week 1. Both groups showed similar incidences of treatment emergent adverse events (TEAEs, 147 (65.0%) in the fezolinetant group, 138 (61.1%) in the placebo group) and serious TEAEs (10 (4.4%) and 8 (3.5%), respectively). The most common TEAEs in the fezolinetant group were covid-19 (30 (13.3%)), headache (20 (8.8%)), and fatigue (13 (5.8%)).

CONCLUSIONS

Fezolinetant was efficacious and well tolerated over a six month period for treating moderate-severe vasomotor symptoms in individuals considered unsuitable for hormone therapy. These results highlight the utility of fezolinetant as an effective treatment option for those who have contraindications to or choose not to use hormone therapy.

TRIAL REGISTRATION

ClinicalTrials.gov NCT05033886; EudraCT 2021-001685-38.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Hormone therapy is an effective treatment for vasomotor symptoms associated with menopause

Treatment is not always appropriate, however, and hormone therapy is unsuitable for many individuals

Fezolinetant, an oral, non-hormonal, neurokinin 3 receptor antagonist treatment option for moderate-severe vasomotor symptoms, is approved in many countries, including the US, Europe, and Australia, at a dose of 45 mg once daily

WHAT THIS STUDY ADDS

Fezolinetant 45 mg once daily was efficacious and well tolerated as a treatment for moderate-severe vasomotor symptoms in individuals considered unsuitable candidates for hormone therapy

Improvements in moderate-severe vasomotor symptoms were observed as early as week 1, with sustained benefit throughout the 24 week treatment period

No safety signals of concern, including drug induced liver injury, were observed

Introduction

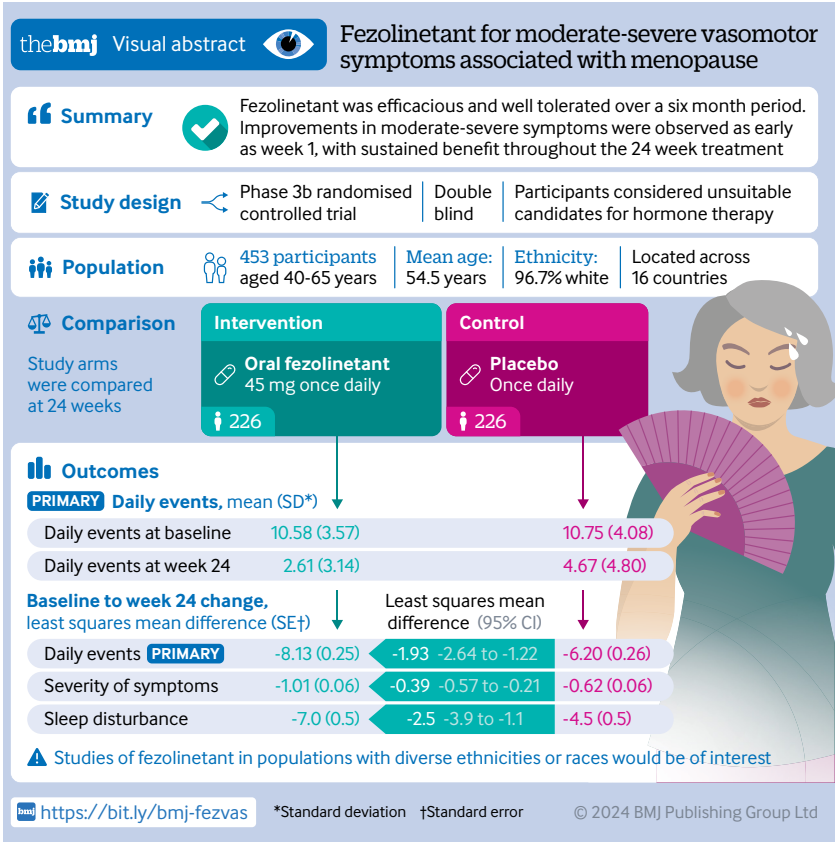
Vasomotor symptoms, comprising hot flushes and night sweats, are the most common and bothersome symptoms associated with menopause.[1 2] Up to 80% of women experience vasomotor symptoms during menopause.[1 2] Moderate-severe symptoms occur in 11-46% of women older than 40 years,[3-5] with a median total duration around 7.4 years,[6] whereas the severity of vasomotor symptoms associated with menopause

varies throughout the course of menopause and among women.[3-5]

Although vasomotor symptoms are common and often severe enough to warrant medical treatment, approved and effective non-hormonal treatments are limited. Hormone therapy is effective but not appropriate for everyone.[7] Treatment is contraindicated in women with a history of breast cancer, uterine cancer, active liver disease, or thromboembolic diseases, and caution is advised in those with comorbidities such as cardiovascular disease, diabetes, and raised triglyceride levels.[8] Hormone therapy is not suitable for many women, and some choose not to use it.[9]

Contraindications to hormone therapy in daily practice is important. Individuals may require counselling from their doctor or other healthcare professionals, and risk factors can complicate the treatment decision making process. In addition to having contraindications, many individuals are cautious about or would prefer to not use hormone therapy, despite being suitable candidates for treatment. Reasons for not wanting to use treatment can include worries about side effects or long term risks of treatment, or acceptance that menopause is a transitory, self-limiting condition that does not require treatment.[10] The US Food and Drug Administration has approved low dose paroxetine, a selective serotonin reuptake inhibitor (SSRI), as the only non-hormonal alternative, which offers modest relief of vasomotor symptoms associated with menopause and carries a black box warning for suicidal thoughts and behaviour and other side effects.[11] Alternative non-hormonal drug options include other SSRIs and serotonin and norepinephrine reuptake inhibitors, which are prescribed for up to one fifth of women with vasomotor symptoms.[12 13] The α adrenergic agonist clonidine and neuromodulators such as gabapentin and pregabalin are also non-hormonal options for treating vasomotor symptoms, although they are not globally approved for such management.[8 14] The Menopause Society does not recommend clonidine owing to adverse events or pregabalin because of the potential for misuse as a schedule V controlled substance. Gabapentin includes black box warnings for rare suicidal thoughts or behaviours.[14] Nutraceutical options for vasomotor symptoms associated with menopause, such as phytoestrogens and herbal derivatives, are widely available as an alternative to hormone therapy, but evidence of their efficacy is limited.[15] None of these other potential treatments is approved globally to manage vasomotor symptoms. A substantial unmet need therefore exists for safe and effective options for non-hormonal treatment of vasomotor symptoms associated with menopause.[16 17]

Fezolinetant, an oral, non-hormonal, neurokinin 3 receptor antagonist, is a treatment option for moderate-severe vasomotor symptoms, and it is approved in many countries, including the US, Europe, and Australia at a dose of 45 mg once daily.[18-22] Fezolinetant blocks neurokinin B signalling, normalising kisspeptin, neurokinin B, and dynorphin neuron activity in the thermoregulatory centre of the brain to reduce the frequency and severity of vasomotor symptoms.[23 24] Fezolinetant was shown to be efficacious and well tolerated for treating moderate-severe vasomotor symptoms associated with menopause in phase 3 studies SKYLIGHT 1 and SKYLIGHT 2,[25 26] which both included a 12 week placebo control period followed by active treatment extension to 52 weeks. To further investigate the clinical benefits of fezolinetant for the treatment of moderate-severe vasomotor symptoms, we performed a phase 3b trial (DAYLIGHT), which included a 24 week placebo control period and enrolled a population considered unsuitable for hormone therapy.



Methods

Study design, objectives, and participants

The present study was a phase 3b, randomised, double blind, placebo controlled trial to assess the efficacy and safety of fezolinetant for treating moderate-severe vasomotor symptoms associated with menopause in individuals considered unsuitable for hormone therapy. Written informed consent was obtained from all participants before any study related procedures. We aimed to evaluate the efficacy of fezolinetant 45 mg versus placebo once daily on the frequency (primary endpoint) and severity (secondary) of moderate-severe vasomotor symptoms and patient reported sleep disturbance

(secondary) associated with menopause. Participants were provided with a reference guide for severity of symptoms: mild—sensation of heat without sweating; moderate—sensation of heat with sweating, able to continue activity; and severe—sensation of heat with sweating, unable to continue activity.

Individuals aged 40-65 years with moderate-severe vasomotor symptoms associated with menopause and considered unsuitable candidates for hormone therapy were randomised 1:1 using interactive response technology to fezolinetant 45 mg or placebo once daily and stratified by smoking status (current and non-smoker (former or never)). Categories for hormone therapy unsuitability were defined based on contraindicated; caution (based on medical history); stoppers (previous discontinuation of hormone therapy owing to lack of efficacy, side effects, or medical advice); or averse (informed choice not to use hormone therapy after discussion with a clinician) (see supplementary table 1).

Endpoints

The primary efficacy endpoint was mean change in the frequency of moderate-severe vasomotor symptoms from baseline to week 24. The key secondary efficacy endpoint was mean change in severity of moderate-severe vasomotor symptoms from baseline to week 24. The selected secondary endpoint was mean change in the Patient-Reported Outcome Measurement Information System (PROMIS) Sleep Disturbance Short Form 8b total score from baseline to week 24. PROMIS is a set of patient centred instruments that evaluates physical, mental, and social health.[27] PROMIS Sleep Disturbance Short Form 8b was developed from PROMIS to assess sleep disturbance, and it evaluates difficulties and problems with falling asleep, staying asleep, and getting enough sleep, as well as perceptions of the quality and satisfaction of sleep. Exploratory endpoints included two Patient Global Impression of Change measures, one for vasomotor symptoms and one for sleep disturbance, and menopause specific quality of life, measured at baseline and weeks 4, 12, 16, and 24. The Patient Global Impression of Change in Sleep Disturbance is a patient reported one item questionnaire that asks participants to rate the severity of any problems during nighttime sleeping using a scale from 1 (no problems) to 4 (severe problems). The questionnaire asks participants to rate how well they were sleeping at that timepoint compared with the start of the study, using a scale from 1 (much better) to 7 (much worse). Similarly, using the same scale the Patient Global Impression of Change in Vasomotor Symptoms asks participants to rate the severity of their vasomotor symptoms compared with the start of the study.

Safety was assessed based on treatment emergent adverse events (TEAEs). A TEAE was defined as an adverse event observed between start of the study drug and up to 21 days after the last dose. Safety follow-up visits were scheduled for three weeks from the last dose. The number and percentage of participants with TEAEs, drug related TEAEs, serious TEAEs, drug related serious TEAEs, TEAEs leading to withdrawal of the study intervention, and drug related TEAEs leading to withdrawal of study intervention were summarised by system organ class, Medical Dictionary for Regulatory Activities version 25.0 preferred term, and treatment group. We also summarised the number and percentage of TEAEs by severity and causality. Participants who discontinued treatment early were asked to remain in the study and continue to complete the daily electronic diary of vasomotor symptoms and electronic patient reported outcome assessments as scheduled to week 24. They were monitored for adverse events, serious adverse events, and use of concomitant drugs to week 27.

Liver function and liver injury were evaluated as part of standard monitoring investigations, including previous phase 3 studies[25 26] of fezolinetant. An independent panel of three liver experts (liver safety monitoring panel) evaluated participants for potential drug induced liver injury who met the criterion of alanine transaminase (ALT) or aspartate aminotransferase (AST) greater than three times the upper limit of normal (ULN) or total bilirubin more than twice the ULN.

Transvaginal ultrasonography was required for all participants to assess endometrial thickness at screening and week 24 or end of treatment, or at

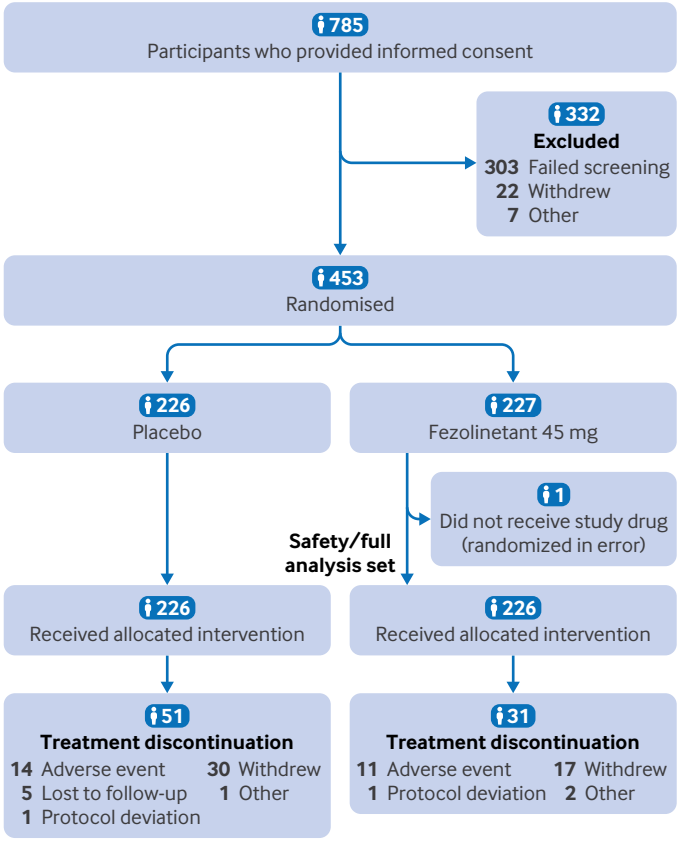


Fig 1 | Flow chart of participants through study. Safety and full analysis sets were defined as all participants who were randomised and received at least one dose of study drug

the early discontinuation visit for participants who stopped prematurely.

Statistical analysis

All safety analyses were performed using the safety analysis set, defined as all participants who were randomised and received at least one dose of study intervention. All primary, secondary, and exploratory efficacy analyses were performed using the full analysis set, defined as all participants who were randomised and received at least one dose of study intervention. For both sets, participants were analysed according to the treatment group to which they were randomised.

For a pairwise comparison of the primary endpoint using a two sample *t* test at a two sided 5% α, we determined that 220 participants in each group would provide at least 80% power to detect a difference from placebo of −1.8, assuming a standard deviation (SD) of 5.6. This size was calculated assuming that about 30% of participants might discontinue the study prematurely. For a pairwise comparison of the key secondary endpoint using a two sample *t* test at a two sided 5% α, estimated power was calculated as 31% and 59% with 220 participants in each group to detect a difference from placebo of −0.2 and −0.3, respectively, assuming a SD of 1.2. The α statistic was only applied to the key secondary endpoint if the primary endpoint was statistically significant at the 5% level.

We performed a mixed model for repeated measures analysis with a missing at random assumption on change in the average daily frequency (or severity) of moderate-severe vasomotor symptoms from baseline to week 24. For the primary and key secondary efficacy endpoints, the primary analysis method was a mixed model for repeated measures using change from baseline as the dependent variable; treatment group, week, and smoking status (current *v* former or never) as factors; baseline weight and baseline value as covariates; and treatment group by week and baseline value by week as interaction terms. From this analysis, comparisons between fezolinetant and placebo were calculated based on least squares mean contrasts using a two sided 95% confidence interval. PROMIS Sleep Disturbance Short Form 8b total score was analysed using a similar method; however, P values were not controlled for multiplicity.

Patient and public involvement

Public and patient involvement was initiated following the optional exit interviews available to participants and study coordinators after the phase 2 dose finding study (NCT03192176). The interviews were largely focused on the technology used in the study. The technology was revised based on the participant's feedback. The same participants were asked to re-evaluate the electronic vasomotor symptoms diary for improvement before initiation of the phase 3 studies, including DAYLIGHT, to confirm the changes made were effective.

Results

Baseline characteristics

The study was conducted between 8 November 2021 and 20 April 2023 at 69 centres in 16 countries (Canada, the Netherlands, Belgium, France, Spain, Finland, Hungary, Italy, Czech Republic, UK, Denmark, Sweden, Norway, Poland, Germany, and Turkey). Overall, the centres randomised 453 participants (fezolinetant n=227, placebo n=226), with 370 (81.7%) completing the study (195 and 175, respectively) (fig 1). The safety analysis and full analysis sets, defined as all participants who were

Table 1 | Baseline characteristics of participants. Values are number (percentage) unless stated otherwise

Characteristics	Fezolinetant (n=226)	Placebo (n=226)	Total (n=452)
Mean (SD) age (years)	54.9 (4.8)	54.1 (4.6)	54.5 (4.7)
Mean (SD) weight (kg)	74.2 (12.6)	72.6 (13.2)	73.4 (12.9)
Mean (SD) BMI	27.42 (4.33)	26.98 (4.52)	27.20 (4.43)
BMI category:			
<25	67 (29.6)	85 (37.6)	152 (33.6)
≥25	159 (70.4)	141 (62.4)	300 (66.4)
Race:			
White	217 (96.0)	218 (97.3)	435 (96.7)
Other*	9 (4.0)	6 (2.7)	15 (3.3)
Missing	0	2	2
Categories for hormone therapy unsuitability†:			
Contraindicated	27 (11.9)	23 (10.2)	50 (11.1)
Caution	74 (32.7)	91 (40.3)	165 (36.5)
Stoppers	32 (14.2)	37 (16.4)	69 (15.3)
Averse	93 (41.2)	75 (33.2)	168 (37.2)
Smoking status‡:			
Current	36 (15.9)	35 (15.5)	71 (15.7)
Former/never	190 (84.1)	191 (84.5)	381 (84.3)

BMI=body mass index; SD=standard deviation.
*Not white, or more than one race.
†Caution=based on medical history, stoppers=previous discontinuation of hormone therapy; averse=informed choice not to use hormone therapy.
‡Current versus former or never smoking status was a stratification factor for randomisation.

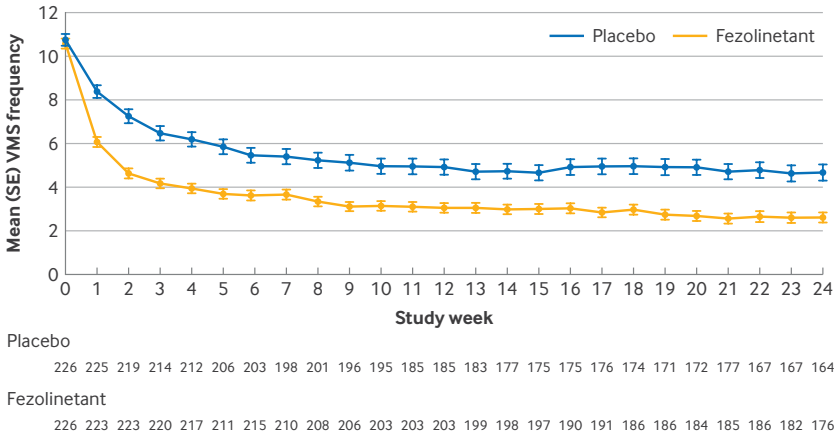


Fig 2 | Daily change in frequency of moderate-severe vasomotor symptoms associated with menopause from baseline to week 24. SE=standard error; VMS=vasomotor symptoms

randomised and received at least one dose of study drug, comprised 452 participants (fezolinetant n=226, placebo n=226), as one participant randomised to the fezolinetant group did not receive study drug. Of these, 387 (85.6%) participants completed the 24 week treatment period. Results are presented for the 452 participants in the safety and full analysis sets.

Eighty two (18.1%) participants discontinued treatment owing to adverse events (n=25, 5.5%), loss to follow-up (n=5, 1.1%), protocol deviation (n=2, 0.4%), withdrawal from study (n=47, 10.4%), and other reasons (n=3, 0.7%). Of the 47 (10%) participants who withdrew from treatment, 17 (8%) were assigned to fezolinetant and 30 (13%) to placebo. All five participants lost to follow-up were in the placebo group; one participant completed treatment with the last dose in week 24 but did not return for the safety follow-up, and the other four participants discontinued early but no reason was provided. Mean (SD) age was 54.5 (4.7) years, and most of the participants were white (n=435, 96.7%) (table 1). Most participants were categorised as either hormone therapy averse (n=168, 37.2%) or caution (n=165, 36.5%); the remainder were contraindicated (n=50, 11.1%) or stoppers (n=69, 15.3%). Mean (SD) overall drug use was 150.8 (44.6) days. Baseline personal

Table 2 | Change from baseline in primary and secondary endpoints

	Fezolinetant (n=226)	Placebo (n=226)
Primary: Frequency of moderate-severe vasomotor symptoms		
Baseline:		
No with data available	226	226
Mean (SD) events daily	10.58 (3.57)	10.75 (4.08)
Week 24:		
No with data available	176	164
Mean (SD) events daily	2.61 (3.14)	4.67 (4.80)
Change from baseline:		
No with data available	176	164
Mean (SD) events daily	−8.15 (4.43)	−6.09 (4.19)
Least squares mean* (SE)	−8.13 (0.25)	−6.20 (0.26)
Least squares mean (SE) difference†; P value‡	−1.93 (0.36); <0.001	
Secondary: Severity of moderate-severe vasomotor symptoms		
Baseline:		
No with data available	226	226
Mean (SD) severity	2.43 (0.36)	2.41 (0.34)
Week 24:		
No with data available	176	164
Mean (SD) severity	1.43 (0.97)	1.87 (0.82)
Change from baseline:		
No with data available	176	164
Mean (SD) severity	−0.99 (0.97)	−0.54 (0.80)
Least squares mean* (SE)	−1.01 (0.06)	−0.62 (0.06)
Least squares mean (SE) difference†; P value‡	−0.39 (0.09); <0.001	
Secondary: Change from baseline in PROMIS SD-SF 8b total score to week 24		
Baseline:		
No with data available	224	225
Mean (SD) score	28.3 (6.1)	27.6 (6.3)
Week 24:		
No with data available	197	178
Mean (SD) score	20.9 (7.3)	22.5 (7.8)
Change from baseline:		
No with data available	196	178
Mean (SD) score	−7.3 (7.7)	−4.6 (8.1)
Least squares mean* (SE)	−7.0 (0.5)	−4.5 (0.5)
Least squares mean (SE) difference†; unadjusted P value‡	−2.5 (0.7); <0.001	

PROMIS-SD-SF=Patient-Reported Outcome Measurement Information System Sleep Disturbance Short Form; SD=standard deviation; SE=standard error.
*Least square mean estimated from mixed model for repeated measures. A negative change indicates a reduction from baseline (ie, a favourable outcome).
†Fezolinetant minus placebo.
‡Two sided.
Baseline included incidences of moderate and severe vasomotor symptoms, and post-baseline included incidences of mild, moderate, and severe symptoms.

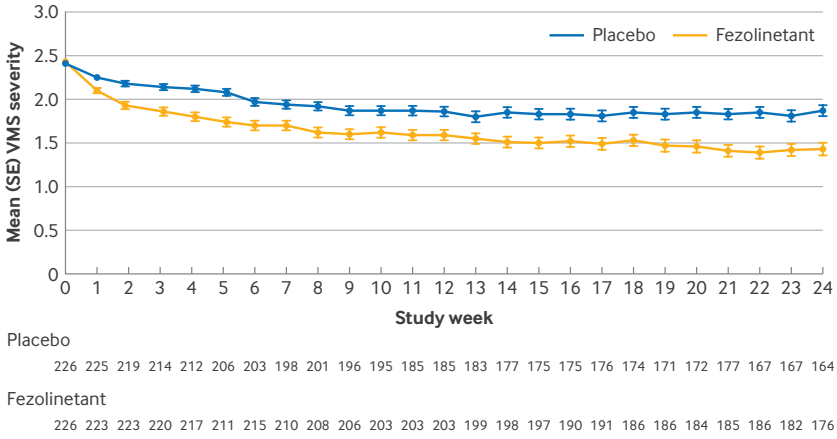


Fig 3 | Daily change in mean severity of moderate-severe vasomotor symptoms associated with menopause from baseline to week 24. SE=standard error; VMS=vasomotor symptoms

characteristics were generally similar between the two treatment groups.

Primary endpoint

In the 226 participants assigned to fezolinetant, mean frequency of vasomotor symptoms reduced from 10.58 (SD 3.57) events daily at baseline to 2.61 (3.14) at week 24 (fig 2). In the 226 participants assigned to placebo, mean frequency of vasomotor symptoms reduced from 10.75 (SD 4.08) events daily at baseline to 4.67 (4.80) at week 24. Fezolinetant significantly reduced the frequency of vasomotor symptoms compared with placebo at week 24 (least squares mean difference −1.93, 95% confidence interval (CI) −2.64 to −1.22; P<0.001) (table 2). At week 24 the least squares mean percentage change from baseline was −75.66% (95% CI −80.13% to −71.19%) for fezolinetant and −59.12% (−63.71% to −54.52%) for placebo. This significant reduction in frequency of vasomotor symptoms started

Table 3 | Change from baseline in exploratory endpoints. Values are number* (percentage) unless stated otherwise

Analysis visit	Fezolinetant (n=226)	Placebo (n=226)
Exploratory: Change from baseline in PGI-C VMS to week 24		
Week 24:		
No with available data	197	178
Much better	123 (62.4)	71 (39.9)
Moderately better	32 (16.2)	22 (12.4)
A little better	19 (9.6)	19 (10.7)
No change	17 (8.6)	54 (30.3)
A little worse	3 (1.5)	3 (1.7)
Moderately worse	1 (0.5)	5 (2.8)
Much worse	2 (1.0)	4 (2.2)
P value†	<0.001	
Exploratory: Change from baseline in PGI-C SD to week 24		
Week 24		
No with available data	197	178
Much better	74 (37.6)	42 (23.6)
Moderately better	46 (23.4)	30 (16.9)
A little better	21 (10.7)	30 (16.9)
No change	50 (25.4)	62 (34.8)
A little worse	4 (2.0)	7 (3.9)
Moderately worse	2 (1.0)	2 (1.1)
Much worse	0 (0.0)	5 (2.8)
P value†	<0.001	
Exploratory: Change from baseline in MENQOL total score to week 24		
Baseline:		
No with available data	224	223
Mean (SD) score	4.53 (1.38)	4.46 (1.39)
Week 24:		
No with available data	197	178
Mean (SD) score	2.84 (1.40)	3.22 (1.55)
Change from baseline:		
No with available data	196	176
Mean (SD) score	−1.68 (1.50)	−1.26 (1.34)
Least squares mean* (SE)	−1.66 (0.09)	−1.22 (0.09)
Least squares mean (SE) difference‡; unadjusted P value§	−0.44 (0.13); <0.001	

MENQOL=Menopause-specific Quality of Life; PGI-C SD=Patient Global Impression of Change in Sleep Disturbance; PGI-C VMS=Patient Global Impression of Change in Vasomotor Symptoms; SD=standard deviation; SE=standard error.
The least squares means, SEs, and P values for MENQOL came from a mixed model repeated measurements analysis of covariance model, with change from baseline as the dependent variable and treatment group, week and smoking status (current *v* former/never) as factors, baseline weight and baseline value as covariates, and treatment group by week and baseline value by week as interaction terms.
*Participants with available data at each visit and used as the denominator for PGI-C estimates.
†Obtained using Cochran-Mantel-Haenszel test with modified ridit scores.
‡Difference=fezolinetant minus placebo.
§P value is for comparison of fezolinetant with placebo from the mixed model repeated measurements described above. For change from baseline in total score, a negative value (decrease from baseline) indicates a better outcome.

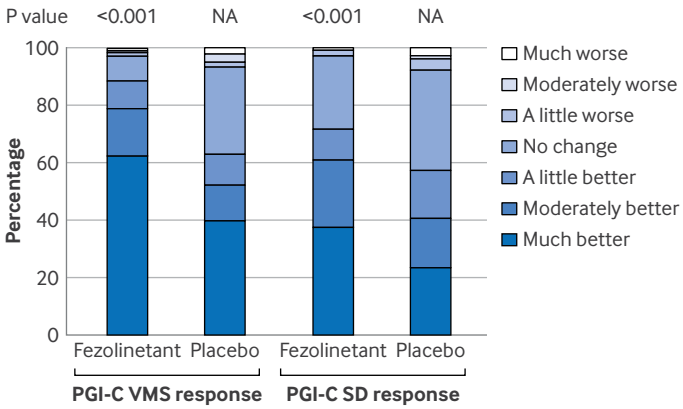


Fig 4 | Distribution of PGI-C VMS and PGI-C SD at week 24 in individuals with moderate-severe vasomotor symptoms associated with menopause. NA=not available; PGI-C SD=Patient Global Impression of Change in Sleep Disturbance; PGI-C VMS=Patient Global Impression of Change in Vasomotor Symptoms

on day 1 (see supplementary figure S1) and continued to week 24 (fig 2).

Secondary endpoints

In the 226 participants assigned to fezolinetant, severity of vasomotor symptoms reduced from a mean 2.43 (SD 0.36) at baseline to 1.43 (0.97) at week 24 (fig 3). In the 226 participants assigned to placebo, severity of vasomotor symptoms reduced from a mean 2.41 (0.34) at baseline to 1.87 (0.82) at week 24. The week 24 difference in symptom severity between fezolinetant and placebo was significant (least squares mean difference −0.39, 95% CI −0.57 to −0.21; P<0.001) (table 2). Participants receiving fezolinetant also had a greater reduction in total scores on the PROMIS Sleep Disturbance Short Form 8b compared with the placebo group (least mean squares mean difference −2.5, −3.9 to −1.1; P<0.001) (table 2).

Exploratory endpoints

At week 24, the most common response on the Patient Global Impression of Change in Vasomotor Symptoms in participants receiving fezolinetant was "much better" (n=123, 62.4% *v* n=71, 39.9%, fezolinetant *v* placebo groups, respectively, P<0.001) (table 3 and fig 4). Similarly, at week 24, the most common response on the Patient Global Impression of Change in Sleep Disturbance in participants receiving fezolinetant was "much better" (n=74, 37.6% *v* n=42, 23.6%, fezolinetant *v* placebo groups, respectively, P<0.001) (table 3, figure 4). Participants receiving fezolinetant also had greater reductions from baseline (improvements) in mean menopause specific quality of life total score relative to placebo at week 24 (least squares mean difference −0.44, −0.69 to −0.18; P<0.001) (table 3).

Table 4 | Overview of TEAEs

	No (%)	
	Fezolinetant (n=226)	Placebo (n=226)
TEAE	147 (65.0)	138 (61.1)
Drug related TEAE*	39 (17.3)	25 (11.1)
Serious TEAE	10 (4.4)	8 (3.5)
Drug related serious TEAE*	1 (0.4)	0
Drug related TEAE leading to death*	0	0
TEAE leading to withdrawal of treatment	11 (4.9)	14 (6.2)
Drug related TEAE leading to withdrawal of treatment*	7 (3.1)	7 (3.1)
Death	0	0

TEAE=treatment emergent adverse event.
*If an association was missing, it was considered as drug related.

Safety

No differences were found in incidence of TEAEs (fezolinetant: n=147, 65.0%; placebo: n=138, 61.1%) and serious TEAEs (n=10, 4.4%; n=8, 3.5%, respectively) between the groups (table 4). The most common TEAEs in the fezolinetant group were covid-19 (n=30, 13.3%), headache (n=20, 8.8%), and fatigue (n=13, 5.8%) (table 5). The most common TEAEs in the placebo group were covid-19 (n=29, 12.8%), headache (n=21, 9.3%), and nasopharyngitis (n=11, 4.9%). There was one (0.4%) reported TEAE of system organ class neoplasms benign, malignant, and unspecified (including cysts and polyps) of mild severity in the placebo group, which was considered unrelated to placebo, and no TEAEs of this system organ class reported in the fezolinetant group.

Increases in abnormal liver test results were reported for 10 (4.4%) participants in the fezolinetant group and six (2.7%) in the placebo group (table 6). For liver safety assessments, three (1.3%) participants in the fezolinetant group showed ALT levels three times the ULN (table 7). The liver safety monitoring panel concluded a causal association was possible in one of the participants and unlikely in the other two participants. No participants showed AST levels three times the ULN or total bilirubin twice the ULN. While there were transient or isolated increases in transaminase levels during the study, no participants had drug induced liver injury according to Hy's law.[28]

TEAEs of special interest included uterine bleeding, which was reported for six (2.7%) participants in the fezolinetant group and 10 (4.4%) in the placebo group (table 6). None of these events was considered serious. In six of 10 participants in the placebo group and four of six in the fezolinetant group, these events were reported as vaginal or postmenopausal bleedings. Eight participants had 11 study drug related events of vaginal or postmenopausal bleeding. Most of these events resolved with no action or resolved after withdrawal of the study intervention, and the outcome of one event (vaginal haemorrhage) was unknown with no action taken. Other TEAEs of special interest included endometrial hyperplasia, cancer, and disordered proliferative endometrium, which was reported by one (0.4%) participant in the fezolinetant group and two (0.9%) participants in the placebo group. All three of these events were preferred terms of endometrial thickening measured

Table 5 | Most common TEAEs occurring in ≥2% of participants in the fezolinetant group

MedDRA preferred term	No (%)	
	Fezolinetant (n=226)	Placebo (n=226)
Covid-19	30 (13.3)	29 (12.8)
Headache	20 (8.8)	21 (9.3)
Fatigue	13 (5.8)	1 (0.4)
Nasopharyngitis	9 (4.0)	11 (4.9)
Nausea	6 (2.7)	4 (1.8)
Diarrhoea	6 (2.7)	3 (1.3)
Upper respiratory tract infection	6 (2.7)	4 (1.8)
Influenza	6 (2.7)	6 (2.7)
Dizziness	6 (2.7)	5 (2.2)
Insomnia	6 (2.7)	1 (0.4)
Anxiety	6 (2.7)	2 (0.9)
Urinary tract infection	5 (2.2)	5 (2.2)
Bronchitis	5 (2.2)	3 (1.3)
Weight increase	5 (2.2)	1 (0.4)
Oropharyngeal pain	5 (2.2)	2 (0.9)

TEAE=treatment emergent adverse event; MedDRA=Medical Dictionary for Regulatory Activities v25.0.

with transvaginal ultrasound and non-serious, none were related to cancer, and all three were considered study drug related. Thrombocytopenia was a TEAE of special interest and reported in no participants in the fezolinetant group and one (0.4%) participant in the placebo group. It was not considered serious or related to the use of placebo.

Discussion

The findings of this study support evidence[7 9 29 30] that fezolinetant is an effective treatment option for individuals with moderate-severe vasomotor symptoms associated with menopause who cannot or choose not to use hormone therapy. This study provided placebo controlled efficacy data over a 24 week period, compared with 12 weeks in the SKYLIGHT studies.[25 26] Frequency and severity of moderate-severe vasomotor symptoms at week 24 showed statistically significant improvements with fezolinetant 45 mg compared with placebo once daily, a sustained treatment effect over a longer period than in previous studies. In addition to these findings, a greater reduction in patient reported sleep disturbance (PROMIS Sleep Disturbance Short Form 8b total score) was seen in the fezolinetant compared with placebo group.

Table 6 | TEAEs of special interest

MedDRA preferred term	No (%)	
	Fezolinetant (n=226)	Placebo (n=226)
Liver test elevations	10 (4.4)	6 (2.7)
Alanine aminotransferase increased	4 (1.8)	1 (0.4)
γ-glutamyltransferase increased	3 (1.3)	4 (1.8)
Hepatic enzyme increased	3 (1.3)	1 (0.4)
Aspartate aminotransferase increased	1 (0.4)	1 (0.4)
Blood bilirubin increased	1 (0.4)	0
Transminases increased	0	1 (0.4)
Uterine bleeding	6 (2.7)	10 (4.4)
Vaginal haemorrhage	4 (1.8)	6 (2.7)
Uterine haemorrhage	2 (0.9)	1 (0.4)
Menstrual disorder	0	1 (0.4)
Postmenopausal haemorrhage	0	2 (0.9)
Endometrial hyperplasia, cancer, or disordered proliferative endometrium	1 (0.4)	2 (0.9)
Endometrial thickening	1 (0.4)	2 (0.9)
Thrombocytopenia	0	1 (0.4)
Platelet count decreased	0	1 (0.4)

TEAE=treatment emergent adverse event; MedDRA=Medical Dictionary for Regulatory Activities v25.0.

Comparison with other studies

Improvements in frequency of moderate-severe vasomotor symptoms in the fezolinetant group compared with placebo were observed as early as day 1, consistent with efficacy results in phase 3 studies SKYLIGHT 1 and SKYLIGHT 2.[25 26] The available safety data appeared generally consistent with the known safety profile for fezolinetant, including data from phase 3 placebo controlled trials showing that fezolinetant is well tolerated for as much as 52 weeks.[25 26 31] The incidence of serious TEAEs from baseline to week 24 was low. No safety signals of concern were observed, including liver safety, in the fezolinetant group, and no drug induced liver injury was observed in any study participants. Some participants experienced an increase in transaminase levels, which overall were not serious, and asymptomatic liver test abnormalities, captured through protocol specified routine testing. Three participants in the fezolinetant group had raised ALT levels three times the ULN; none of them was accompanied by bilirubin levels twice the ULN. The liver safety monitoring panel concluded that a causal association was possible in one participant and unlikely in the other two participants.

Strengths and weaknesses of this study

The findings of this study add to a large body of data showing a positive benefit-risk profile for fezolinetant and the potential of this drug to address an important unmet need for individuals with moderate-severe vasomotor symptoms associated with menopause. The study included a longer placebo control period (24 weeks) than previous phase 3 studies, and a large defined patient population unsuitable for current hormone therapy (ie, hormone therapy contraindicated, caution, stoppers, and averse).[25 26] A potential limitation of this study was that participants were from 16 countries (Canada, the Netherlands, Belgium, France, Spain, Finland, Hungary, Italy, Czech Republic, UK, Denmark, Sweden, Norway, Poland, Germany, and Turkey), with most self-identifying as white. Further studies of fezolinetant in global populations with diverse ethnicity or races would be of interest.

Conclusion

The findings of this study support the utility of fezolinetant as an effective non-hormonal treatment option for individuals who cannot or choose not to use hormone therapy for the management of moderate-severe vasomotor symptoms associated with menopause.

Table 7 | Liver safety assessments

Analyte* and criteria	No (%) Fezolinetant (n=226)	Placebo (n=226)
ALT		
>3×ULN	3/224 (1.3)	0/220
>5×ULN	1/224 (0.4)	0/220
>8×ULN	1/224 (0.4)	0/220
>10×ULN	1/224 (0.4)	0/220
>20×ULN	0/224	0/220
AST		
>3×ULN	0/224	0/220
>5×ULN	0/224	0/220
>8×ULN	0/224	0/220
>10×ULN	0/224	0/220
>20×ULN	0/224	0/220
ALT or AST		
>3×ULN	3/224 (1.3)	0/220
>5×ULN	1/224 (0.4)	0/220
>8×ULN	1/224 (0.4)	0/220
>10×ULN	1/224 (0.4)	0/220
>20×ULN	0/224	0/220
Total bilirubin		
>2×ULN	0/224	0/220
Alkaline phosphatase		
>1.5×ULN	3/224 (1.3)	1/220 (0.5)
ALT and/or AST + total bilirubin†		
>3×ULN + >2×ULN	0/224	0/220
>3×ULN + >1.5×ULN	0/224	0/220
ALT and/or AST + alkaline phosphatase + total bilirubin†		
>3×ULN + <2×ULN + >2×ULN	0/224	0/220

Denominators show the number of participants who had at least one non-missing value during treatment.
ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal range.
*Maximum value during treatment is presented for each liver enzyme and total bilirubin.
†Combination of values measured on same day or one day apart.

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Ethical approval: This study 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 ethical, scientific, and medical appropriateness of the study before data collection at each site: Canada: Advarra IRB (Ontario, Canada); Netherlands: Medical Research Ethics Committees United (MEC-U), St Antonius Ziekenhuis (Nieuwegein, Netherlands); Belgium: EC of UZ Gent, Medical Ethics Committee, University Hospital Gent (Gent, Belgium); France: Comité de Protection des Personnes Sud-Ouest et Outre-Mer 1, Regional Health Agency (Toulouse, France); Spain: EC Gregorio Marañón, Secretaría Técnica CEIm, Fundación para la Investigación Biomédica Hospital Gregorio Marañón, Pabellón de Gobierno (Madrid, Spain); Finland: Ethics Committee of Hospital District of Northern Savo, Kuopio University Hospital (Kuopio, Finland); Hungary: Medical Research Council (Budapest, Hungary); Italy: CEC, Comitato Etico Referente Area di Pavia Fondazione IRCCS Policlinico "San Matteo" (Pavia, Italy); Czech Republic: Etická komise pro multicentrická klinická hodnocení Fakultní nemocnice, Královské Vinohrady (Prague, Czech Republic); UK: London – Westminster Research Ethics Committee (Nottingham, UK); Denmark: Den Videnskabsetiske Komité for Region Nordjylland Regionssekretariatet (Aalborg, Denmark); Sweden: Etikprövningsmyndigheten (Uppsala, Sweden); Norway: REK sør-øst (Oslo, Norway); Poland: Komisja Bioetyczna przy Okregowej Izbie Lekarskiej w Lublinie (Lublin, Poland); Germany: Ethikkommission der Fakultät für Medizin der Technischen Universität (Munich, Germany); Turkey: Ankara University Tip Fakultesi, Clinical Trial Ethics Committee (Ankara, Turkey). Written informed consent was obtained from all participants before any study related procedures.

Data sharing: Researchers may request access to anonymised 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.

Transparency: The manuscript's guarantor (KS) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: The clinical study report synopsis and plain language summary have been posted on the Astellas clinical trials website (https://www.clinicaltrials.astellas.com). In addition, the plain language summary has been posted on the multi-sponsor website, trial results summaries (https://www.trialsummaries.com/Home/LandingPage). DAYLIGHT findings have been submitted as part of the evidence base for health technology assessment processes, which include critical participation and input from individuals with vasomotor symptoms associated with menopause.

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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;96:1226-35. doi:10.2105/AJPH.2005.066936
2 Williams RE, Kalilani L, DiBenedetti DB, et al, Frequency and severity of vasomotor symptoms among peri- and postmenopausal women in the United States. *Climacteric* 2008;11:32-43. doi:10.1080/13697130701744696
3 Whiteley J, Wagner JS, Bushmakin A, Kopenhafer L, Dibonaventura M, Racketa J. Impact of the severity of vasomotor symptoms on health status, resource use, and productivity. *Menopause* 2013;20:518-24. doi:10.1097/GME.0b013e31827d38a5
4 Blümel JE, Chedraui P, Baron G, et al, Collaborative Group for Research of the Climacteric in Latin America (REDLINC). A large multinational study of vasomotor symptom prevalence, duration, and impact on quality of life in middle-aged women. *Menopause* 2011;18:778-85. doi:10.1097/gme.0b013e318207851d
5 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;21:924-32. doi:10.1097/GME.0000000000000196
6 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;175:531-9. doi:10.1001/jamainternmed.2014.8063
7 Manson JE, Chlebowski RT, Stefanick ML, et al, Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA* 2013;310:1353-68. doi:10.1001/jama.2013.278040
8 Stuenkel CA, Davis SR, Gompel A, et al, Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2015;100:3975-4011. doi:10.1210/jc.2015-2236
9 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;28:875-82. doi:10.1097/GME.0000000000001793
10 Nappi RE, Siddiqui E, Todorova L, Rea C, Gemmen E, Schultz NM. Prevalence and quality-of-life burden of vasomotor symptoms associated with menopause: A European cross-sectional survey. *Maturitas* 2023;167:66-74. doi:10.1016/j.maturitas.2022.09.006
11 Noven Therapeutics, LLC. BRISDELLE™ (paroxetine) prescribing information, June 2013.
12 DePree B, Houghton K, Shiozawa A, et al, Treatment and resource utilization for menopausal symptoms in the United States: a retrospective review of real-world evidence from US electronic health records. *Menopause* 2023;30:70-9. doi:10.1097/GME.0000000000002095
13 Stute P, Cano A, Thurston RC, et al, Evaluation of the impact, treatment patterns, and patient and physician perceptions of vasomotor symptoms associated with menopause in Europe and the United States. *Maturitas* 2022;164:38-45. doi:10.1016/j.maturitas.2022.06.008
14 "The 2023 Nonhormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. The 2023 nonhormone therapy position statement of The North American Menopause Society. *Menopause* 2023;30:573-90. doi:10.1097/GME.0000000000002200
15 De Franciscis P, Colacurci N, Riemma G, et al, A nutraceutical approach to menopausal complaints. *Medicina (Kaunas)* 2019;55:544. doi:10.3390/medicina55090544
16 DePree B, Houghton K, DiBenedetti DB, et al, Practice patterns and perspectives regarding treatment for symptoms of menopause: qualitative interviews with US health care providers. *Menopause* 2023;30:128-35. doi:10.1097/GME.0000000000002096
17 Morga A, Ajmera M, Gao E, et al, Systematic review and network meta-analysis comparing the efficacy of fezolinetant with hormone and nonhormone therapies for treatment of vasomotor symptoms due to menopause. *Menopause* 2024;31:68-76. doi:10.1097/GME.0000000000002281
18 European Medicines Agency. Annex I: summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/veoza-epar-product-information_en.pdf
19 Medicines and Healthcare Products Regulatory Agency. Summary of product characteristics. https://mhraproducts4853.blob.core.windows.net/docs/024ce3122f402926d48673943745317aacb48326.
20 Therapeutic Goods Administration. Australian product information - Veoza™ (fezolinetant). https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent=&id=CP-2024-PI-01388-1&d=20240314172310101
21 U.S. Food and Drug Administration. Highlights of prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/216578s003lbl.pdf.
22 Astellas Pharma AG. Veoza™ (fezolinetant). https://www.swissmedic.ch/dam/swissmedic/en/dokumente/marktueberwachung/rmp/fezolinetant_veoza_rmp-summary.pdf.download.pdf/Fezolinetant_Veoza_Public_Risk_Management_Plan_Summary.pdf
23 Depypere H, Lademacher C, Siddiqui E, Fraser GL. Fezolinetant in the treatment of vasomotor symptoms associated with menopause. *Expert Opin Investig Drugs* 2021;30:681-94. doi:10.1080/13543784.2021.1893305
24 Astellas Pharma US. VEOZAHTM. Highlights of prescribing information 2023. https://www.astellas.com/us/system/files/veozah_uspi.pdf
25 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;108:1981-97. doi:10.1210/clinem/dgad058
26 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;401:1091-102. doi:10.1016/S0140-6736(23)00085-5
27 HealthMeasures. PROMIS®. https://www.healthmeasures.net/explore-measurement-systems/promis
28 US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Guidance for Industry. Drug-induced liver injury: premarketing clinical evaluation. Vol 20212009. Accessed 7 Oct 2024. https://www.fda.gov/media/116737/download
29 Bair YA, Gold EB, Zhang G, et al, Use of complementary and alternative medicine during the menopause transition: longitudinal results from the Study of Women's Health Across the Nation. *Menopause* 2008;15:32-43. doi:10.1097/gme.0b013e31813429d6
30 Cumming GP, Currie H, Morris E, Moncur R, Lee AJ. The need to do better - Are we still letting our patients down and at what cost?*Post Reprod Health* 2015;21:56-62. doi:10.1177/2053369115586122
31 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;141:737-47. doi:10.1097/AOG.0000000000005114

Supplementary information: Additional table S1 and figure S1