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ORIGINAL RESEARCH

Safety of Fezolinetant for Treatment of Moderate to Severe Vasomotor Symptoms Due to Menopause: Pooled Analysis of Three Randomized Phase 3 Studies

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ABSTRACT

Introduction: This study evaluated the safety and tolerability of fezolinetant in women with vasomotor symptoms (VMS) due to menopause in a pooled analysis of data from three 52-week phase 3 studies (SKYLIGHT 1, 2, and 4).

Methods: SKYLIGHT 1 and 2 were double-blind, placebo-controlled studies where women (≥ 40 to ≤ 65 years), with moderate to severe VMS (minimum average ≥ 7 hot flashes/day) were randomized to once-daily placebo, fezolinetant 30 mg or 45 mg. After 12 weeks, those on placebo were re-randomized to fezolinetant 30 mg or 45 mg, while those on fezolinetant continued on their assigned dose for 40 weeks. SKYLIGHT 4 was a placebo-controlled, double-blind, 52-week safety study. Safety was assessed by frequency of treatment-emergent adverse events (TEAEs) and endometrial events. TEAEs of special interest included liver test elevations and endometrial hyperplasia or cancer or disordered proliferative endometrium.

Results: Totals of 952 participants receiving placebo, 1100 receiving fezolinetant 45 mg, and 1103 receiving fezolinetant 30 mg took ≥ 1 dose of study medication. TEAEs occurred in 55.3%, 62.9%, and 65.4%, respectively; exposure-adjusted results were consistent with these results. Most frequent TEAEs

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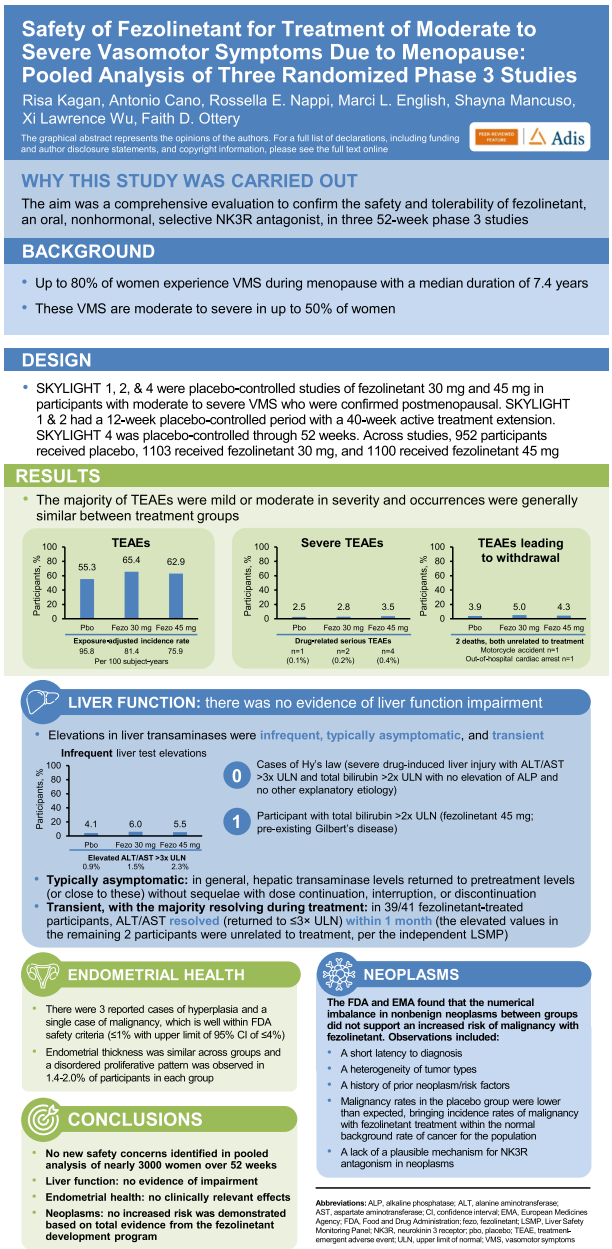
in fezolinetant-treated participants included upper respiratory tract infection (7.7–8.3%), headache (6.8–8.2%), coronavirus disease 2019 (5.8–6.1%), back pain (3.1–3.7%), arthralgia (2.9–3.2%), diarrhea (2.3–3.2%), urinary tract infection (2.9–3.4%), and insomnia (2.0–3.0%). The incidence of drug-related serious TEAEs and associated treatment withdrawals was low. Elevations in liver transaminases occurred in 1.5–2.3% of fezolinetant-treated participants, were typically asymptomatic and transient, resolved on treatment or discontinuation, with no evidence of severe drug-induced liver injury (Hy's law). Endometrial safety results were well within US Food and Drug Administration criteria. Analysis of benign and non-benign neoplasm controlled for exposure demonstrated no increased risk versus placebo.

Conclusion: Pooled data confirm the safety and tolerability of fezolinetant over 52 weeks.

Trial Registration: ClinicalTrials.gov identifiers, NCT04003155, NCT04003142, and NCT04003389. Graphical abstract available for this article.

Graphical Abstract:



Keywords: Fezolinetant; Vasomotor symptoms; Neurokinin 3 receptor antagonist; 52-week safety; Treatment-emergent adverse events; Transa minases; Endometrial hyperplasia

Key Summary Points

Why carry out this study?

Up to 80% of women experience vasomotor symptoms (VMS) during menopause. VMS last for a median duration of 7.4 years and are moderate to severe in up to 50% of individuals.

In two phase 3 trials (SKYLIGHT 1 and 2), the nonhormonal neurokinin 3 receptor antagonist, fezolinetant, reduced the frequency and severity of moderate to severe VMS from baseline to weeks 4 and 12, and this effect was maintained through week 52. SKYLIGHT 4 confirmed the 52-week safety and tolerability of fezolinetant.

The objective of this pre-specified analysis was to evaluate the safety and tolerability of fezolinetant in women with VMS due to menopause using data from a pooled analysis of three 52-week phase 3 studies (SKYLIGHT 1, 2, and 4).

What was learned from the study?

The majority of treatment-emergent adverse events (TEAEs) were not drug-related: the most common events were upper respiratory tract infection, headache, and coronavirus disease 2019, and a similar frequency was observed across the three treatment arms. TEAEs of special interest were infrequently reported in both fezolinetant- and placebo-treated patients.

Overall, fezolinetant demonstrated a favorable safety and tolerability profile over 52 weeks with results consistent with the previously reported individual study findings. The results of this pooled analysis confirm the safety and tolerability of fezolinetant treatment over 52 weeks in nearly 3000 women with VMS due to menopause.

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.27847017.

INTRODUCTION

Vasomotor symptoms (VMS), considered the hallmark of menopause, are defined by hot flashes (also known as hot flushes), night sweats, or both [1]. VMS are reported to be among the most common and bothersome symptoms due to the menopause [1–4], and typically first occur in women aged 40–65 years [1, 5, 6]. Up to 80% of women experience VMS during menopause [3, 7], which last for a median duration of 7.4 years [8] and are moderate to severe in up to 50% of individuals [2, 9, 10]. Differences in the prevalence of VMS are reported across ethnicities and/or geographical regions [1, 5].

Moderate to severe VMS can impair health-related quality of life, adversely influencing sleep quality, concentration/memory, mood, sexual activity, anxiety/depression, total energy levels, and work/leisure activities [9–11]. The primary treatment for moderate to severe VMS due to menopause is hormone therapy (HT) [12–14]. Options for nonhormonal treatment are important as some individuals are not candidates for HT due to contra-indications (e.g., unexplained vaginal bleeding, liver disease, prior estrogen-sensitive cancer, prior coronary heart disease, stroke, myocardial infarction, or venous thromboembolism, or personal history or inherited high risk of thromboembolic disease [12–15]). Other individuals (54–79%) may be eligible but unwilling to receive HT [10].

Fezolinetant is an oral, nonhormonal, selective neurokinin 3 (NK3) receptor antagonist that inhibits neurokinin B binding on kisspeptin/neurokinin B/dynorphin neurons to modulate neuronal activity in the thermoregulatory center [16]. The activity of fezolinetant thereby helps to reduce the signals that trigger

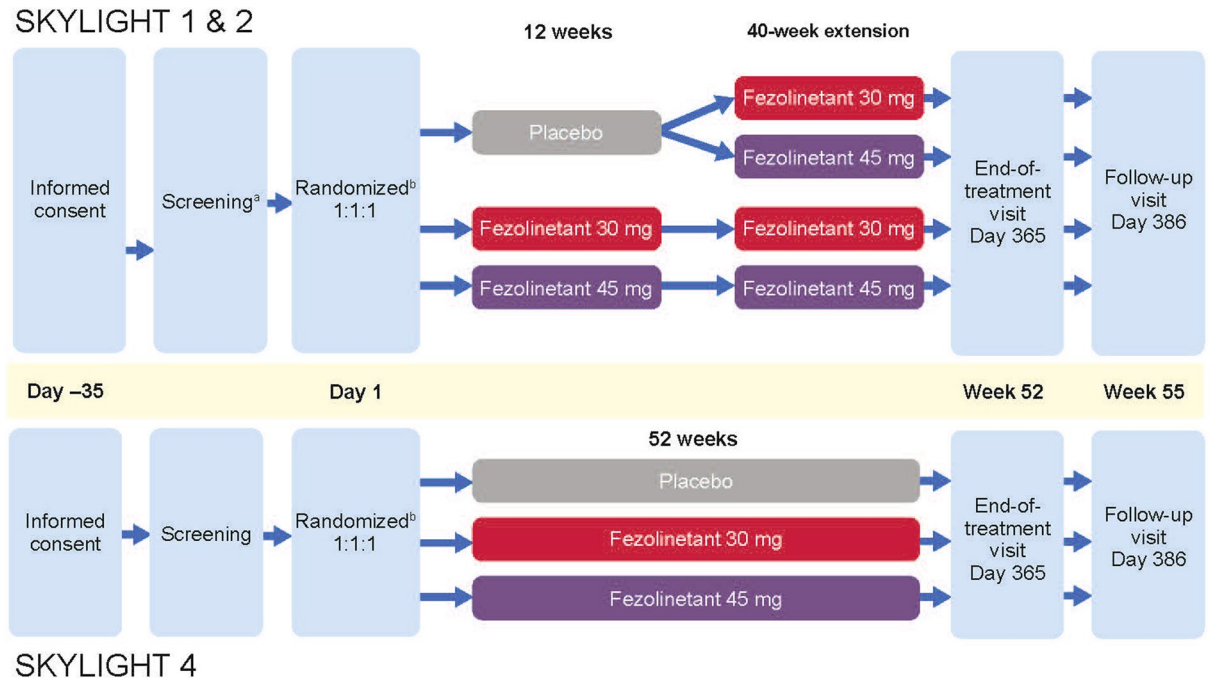


Fig. 1 Study designs: SKYLIGHT 1, 2, and 4. [a]VMS data were collected using an electronic hot flash diary. [b]Smoking status was a randomization stratification factor. *VMS* vasomotor symptoms

a hot flash response. Fezolinetant is approved in many countries, including the United States, Europe, and Australia at a dose of 45 mg once daily [17–21].

The efficacy of fezolinetant was demonstrated in two identical, phase 3 studies, SKYLIGHT 1 (NCT04003155) and 2 (NCT04003142) [22, 23]. In SKYLIGHT 1 and 2, participants with moderate to severe VMS (minimum average of ≥ 7 hot flashes/day or ≥ 50/week) were initially randomized to receive daily doses of placebo, fezolinetant 45 mg, or fezolinetant 30 mg for 12 weeks. The four coprimary efficacy endpoints were met, as fezolinetant statistically significantly reduced the mean change in the daily frequency of moderate to severe VMS from baseline to weeks 4 and 12 and the mean change in the daily severity of moderate to severe VMS from baseline to weeks 4 and 12.

Participants who completed the 12-week placebo-controlled period in SKYLIGHT 1 and 2 entered a 40-week active treatment extension period, where those treated with fezolinetant continued their assigned dose and those on placebo were re-randomized in a blinded fashion to fezolinetant 45 mg or 30 mg. Improvements in VMS frequency and severity were maintained to week 52.

SKYLIGHT 1 and 2 also demonstrated the safety and tolerability of fezolinetant 45 mg and 30 mg, including a low incidence of serious treatment-emergent adverse events (TEAEs) reported in participants with VMS due to menopause [22, 23].

A subsequent phase 3, placebo-controlled, double-blind, 52-week safety study, SKYLIGHT 4 (NCT04003389) was carried out. Participants with VMS were randomized to once-daily placebo, fezolinetant 45 mg, or fezolinetant 30 mg for 52 weeks. SKYLIGHT 4 confirmed the safety and tolerability of fezolinetant [24]. To further demonstrate and understand the totality of safety data across the three phase 3 studies, a pre-specified pooled analysis of SKYLIGHT 1, 2, and 4 data was performed.

METHODS

Compliance with Ethics Guidelines

SKYLIGHT 1, 2, and 4 were conducted in accordance with 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 at each site before data collection. Written informed consent was obtained from all participants before any study-related procedures.

Study Design, Objectives, and Participants

The objective of this pre-specified analysis was to evaluate the safety and tolerability of fezolinetant in women with VMS due to menopause in a pooled analysis of data from three 52-week phase 3 studies (SKYLIGHT 1, 2, and 4) (Fig. 1). Study procedures have been described in detail previously [22–24].

In brief, participants were born female, aged ≥ 40 to ≤ 65 years, and seeking treatment or relief from VMS due to menopause. All participants had a body mass index (BMI) of 18–38 kg/m^2 and confirmed postmenopausal status, defined as one of the following: spontaneous amenorrhea for ≥ 12 consecutive months, spontaneous amenorrhea for ≥ 6 months with biochemical criteria of menopause (follicle-stimulating hormone > 40 IU/L), or bilateral oophorectomy ≥ 6 weeks before the screening visit (with or without hysterectomy). Participants with known or diagnosed non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH) were not excluded, and nor were those with Gilbert's syndrome and elevated total bilirubin, if direct bilirubin, hemoglobin, and reticulocytes were normal. Caffeine use was not restricted.

Data collected and reported separately for SKYLIGHT 1, 2, and 4 [22–24] were subsequently pooled and used as a single dataset for this analysis.

Endpoints

Pre-specified endpoints for this analysis included the frequency of TEAEs and endometrial safety (proportion of participants with endometrial hyperplasia, endometrial malignancy, or disordered proliferative endometrium, and change from baseline to 52 weeks in endometrial thickness). TEAEs, which were collected throughout the studies, were categorized as any TEAEs, as well as drug-related, serious, drug-related serious, leading to withdrawal of treatment, drug-related leading to withdrawal of treatment, and any deaths (unrelated to treatment). Pre-specified TEAEs of special interest were liver test elevations, endometrial hyperplasia or cancer or disordered proliferative endometrium, uterine bleeding, thrombocytopenia, bone fractures, abuse liability, depression, wakefulness, and effect on memory.

Hepatic laboratory assessments were performed by central (and local, if applicable) laboratories; the highest post-baseline value during the treatment period of each liver biochemistry variable was recorded. In addition, an independent liver safety monitoring panel (LSMP) of three independent hepatologists reviewed blinded individual participant cases that had elevated transaminases or other liver safety markers: alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3× upper limit of normal (ULN) or total bilirubin > 2× ULN. Causal relationship to study drug was assessed for each case according to the Drug-induced Liver Injury Network scoring categories, ranging from 1 (Definite), 2 (Highly likely), 3 (Probable), 4 (Possible), 5 (Unlikely), to 6 (Insufficient data) [25].

Transvaginal ultrasounds (TVUs) and endometrial biopsies were performed at screening in participants with a uterus and at week 52/early discontinuation visit and as indicated by relevant TEAEs. For all post-baseline biopsies, the concordance of the three independent expert pathologists was applied: if at least two pathologists agreed, the result was included, but if there was no agreement among the pathologists, the

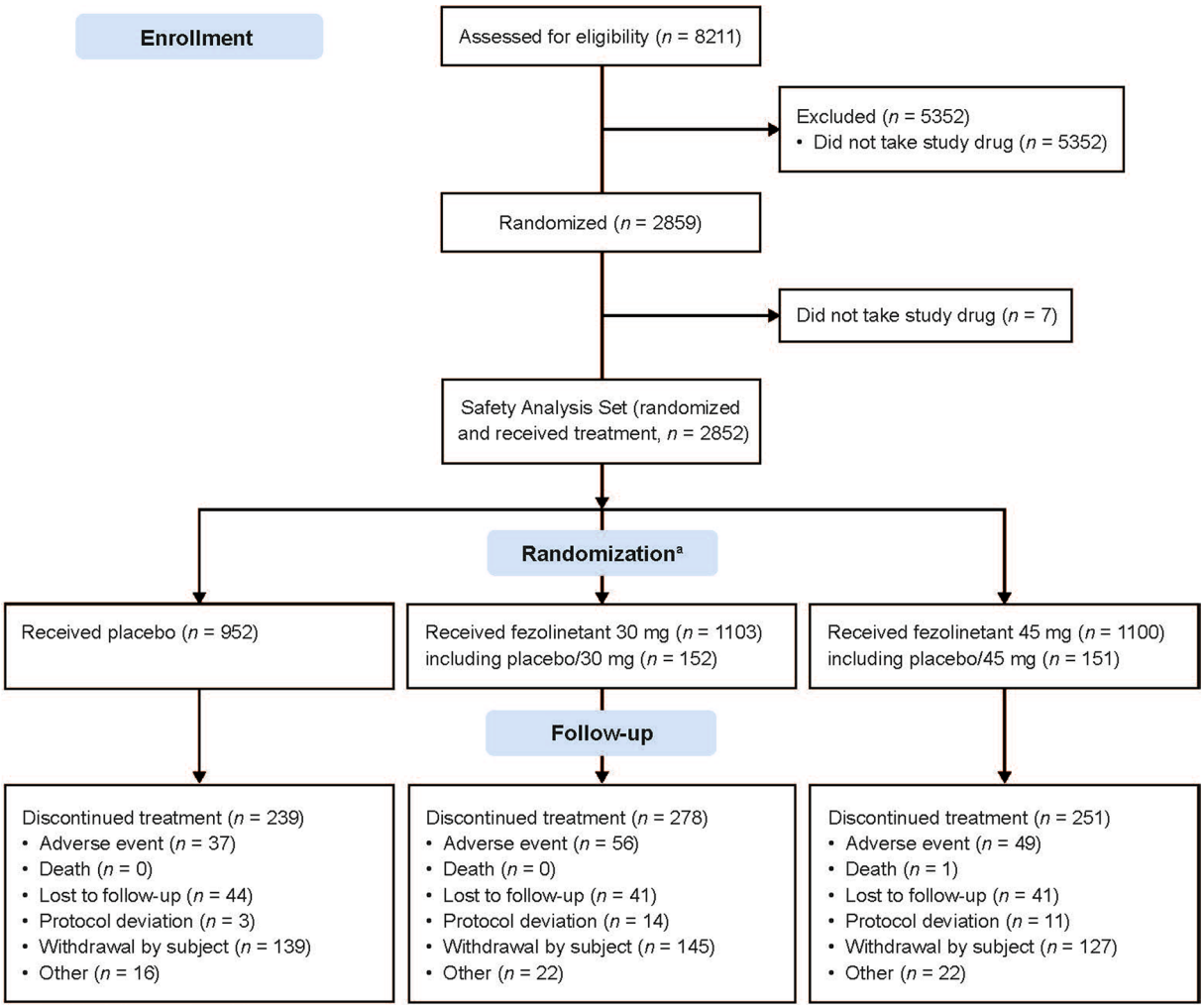


Fig. 2 Patient disposition: SKYLIGHT 1, 2, and 4. The fezolinetant groups included participants who were re-randomized to fezolinetant after 12 weeks on placebo from SKYLIGHT 1 and 2 studies. [a]One participant randomized to fezolinetant 45 mg received 30 mg in first 12 weeks

most severe diagnosis was used as the final diagnosis.

An in-depth post hoc investigation was conducted for any identified malignant neoplasm based on an observed numerical imbalance noted between treatment arms in SKYLIGHT 4. Determination of benign and non-benign was based on the Medical Dictionary for Regulatory Activities (MedDRA) v23.0 High-Level Group Terms under the system organ class: neoplasm benign, malignant, and unspecified (including cysts and polyps).

Statistical Analysis

Analyses were performed in the safety analysis set, which comprised all randomized participants who took at least one dose of study treatment. The fezolinetant groups included placebo participants who were re-randomized to fezolinetant after 12 weeks on placebo from SKYLIGHT 1 and 2 studies. Subgroup analyses were performed for the intrinsic factors of age, race, ethnicity, BMI, NAFLD, and NASH, and diabetic status, and the extrinsic factors of smoking status and geographical region.

Table 1 Key demographics and baseline characteristics (safety analysis set)

	Placebo (*n* = 952)	**Fezolinetant 45 mg[a] (*n* = 1100)**	**Fezolinetant 30 mg[a] (*n* = 1103)**	**Total (*n* = 2852)**
Age in years, mean (SD)	54.8 (4.8)	54.6 (5.0)	54.5 (4.8)	54.6 (4.9)
Race, *n* (%)[b]				
Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Other[c]	24 (2.5)	30 (2.7)	25 (2.3)	72 (2.5)
Black or African American	150 (15.8)	200 (18.2)	192 (17.4)	489 (17.2)
White	778 (81.7)	869 (79.1)	884 (80.3)	2288 (80.3)
Ethnicity, *n* (%)[d]				
Hispanic or Latino	211 (22.2)	240 (21.9)	231 (20.9)	610 (21.4)
Not Hispanic or Latino	739 (77.8)	856 (78.1)	872 (79.1)	2238 (78.6)
BMI in kg/m^2, mean (range)[e]	28.2 (18.3–38.0)	28.2 (18.0–38.0)	28.3 (18.0–38.0)	28.3 (18.0–38.0)
Weight in kg, mean (range)	75.1 (39.0–125.0)	75.3 (45.0–125.0)	75.6 (42.0–123.8)	75.4 (39.0–125.0)
Hysterectomy history, *n* (%)				
Yes	229 (24.1)	274 (24.9)	260 (23.6)	670 (23.5)
No	723 (75.9)	826 (75.1)	843 (76.4)	2182 (76.5)
Smoking status, *n* (%)				
Current	174 (18.3)	196 (17.8)	197 (17.9)	518 (18.2)
Former/never	778 (81.7)	904 (82.2)	906 (82.1)	2334 (81.8)
Alcohol status, *n* (%)				
Current	562 (59.0)	623 (56.6)	636 (57.7)	1665 (58.4)
Former/never	390 (41.0)	477 (43.4)	467 (42.3)	1187 (41.6)
Caffeine use, *n* (%)				
Yes	808 (84.9)	937 (85.2)	944 (85.6)	2424 (85.0)
No	144 (15.1)	163 (14.8)	159 (14.4)	428 (15.0)
Isolated NAFLD, *n* (%)				
Yes	8 (0.8)	7 (0.6)	15 (1.4)	27 (0.9)
No	944 (99.2)	1093 (99.4)	1088 (98.6)	2825 (99.1)
Non-alcoholic steatohepatitis, *n* (%)				
Yes	3 (0.3)	2 (0.2)	2 (0.2)	7 (0.2)
No	949 (99.7)	1098 (99.8)	1101 (99.8)	2845 (99.8)

Table 1 continued

	Placebo (n = 952)	Fezolinetant 45 mg[a] (n = 1100)	Fezolinetant 30 mg[a] (n = 1103)	Total (n = 2852)
Diabetes mellitus, *n* (%)				
Yes	72 (7.6)	93 (8.5)	85 (7.7)	228 (8.0)
No	880 (92.4)	1007 (91.5)	1018 (92.3)	2624 (92.0)
Prior drug-induced liver toxicity, *n* (%)				
Yes	0	0	0	0
No	952 (100.0)	1100 (100.0)	1103 (100.0)	2852 (100.0)

In SKYLIGHT 1, one participant who was randomized to fezolinetant 45 mg group received fezolinetant 30 mg for the first 12 weeks

BMI body mass index, *NAFLD* non-alcoholic fatty liver disease, *SD* standard deviation

[a]The fezolinetant groups included participants who were re-randomized to fezolinetant after 12 weeks on placebo from SKYLIGHT 1 and 2 studies. Participants who initially received placebo in these 2 studies and were included in the 40-week extension period would be included in both the placebo group and one of the fezolinetant groups depending on the re-randomization allocation

[b]Data on race were missing for 1 participant in the fezolinetant 45 mg group and 2 participants in the 30 mg group

[c]Other includes more than 1 race

[d]Data on ethnicity were missing for 2 participants in the placebo group and 4 participants in the fezolinetant 45 mg group

[e]Data on BMI were missing for 1 participant in the placebo group, 2 participants in the fezolinetant 45 mg group, and 1 participant in the fezolinetant 30 mg group

Endometrial health was evaluated using the endometrial health set [safety analysis set participants who had an acceptable biopsy at baseline (at least one endometrial biopsy with satisfactory tissue and no reading of hyperplasia, disordered proliferative pattern, or malignancy)], a post-baseline biopsy within 30 days after the last dose of study intervention, and a satisfactory endometrial biopsy result on day 326 or later or had a post-baseline final diagnosis of hyperplasia, disordered proliferative pattern, or malignancy before day 326. For re-randomized participants, the definition was the same as above, except for day 242 being used instead of day 326.

Summary statistics were generated and presented as frequencies and percentages for categorical data and as mean standard deviation (SD), range, and confidence interval (CI) for continuous data. In addition, exposure-adjusted incidence rate (EAIR), defined as number of subjects with event per 100 subject-years, is presented. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Baseline Demographics

The safety analysis set included 952 participants in the placebo group, 1100 in the fezolinetant 45 mg group, and 1103 in the fezolinetant 30 mg group (Fig. 2). The fezolinetant groups included those participants who were re-randomized to fezolinetant after 12 weeks on placebo from SKYLIGHT 1 and 2 studies.

All treatment groups were similar with respect to demographic and baseline characteristics. Overall, mean (SD) age was 54.6 (4.9) years, 18% of each group were current smokers, 85% were caffeine users, < 1% had isolated NAFLD and no

Table 2 Overview of TEAEs (safety analysis set)

	Placebo (*n* = 952)	Fezolinetant 45 mg[a] (*n* = 1100)	Fezolinetant 30 mg[a] (*n* = 1103)
TEAE, *n* (%) [EAIR[b]]			
Overall	526 (55.3) [95.8]	692 (62.9) [75.9]	721 (65.4) [81.4]
Drug-related	140 (14.7) [25.5]	171 (15.5) [18.7]	161 (14.6) [18.2]
Serious	15[c] (1.6) [2.7]	45[d] (4.1) [4.9]	41[e] (3.7) [4.6]
Drug-related serious	1[f] (0.1) [0.2]	4[g] (0.4) [0.4]	2[h] (0.2) [0.2]
Leading to withdrawal of treatment	37 (3.9) [6.7]	47 (4.3) [5.2]	55 (5.0) [6.2]
Drug-related, leading to withdrawal of treatment	24 (2.5) [4.4]	31 (2.8) [3.4]	25 (2.3) [2.8]
Death—unrelated to treatment, *n* (%) [EAIR[b]]	0	1 (0.1) [0.1]	1 (0.1) [0.1]

COVID-19 coronavirus disease 2019, *EAIR* exposure-adjusted incidence rate, *TEAE* treatment-emergent adverse event

[a]The fezolinetant groups included participants who were re-randomized to fezolinetant after 12 weeks on placebo from SKYLIGHT 1 and 2 studies

[b]Number of subjects with event per 100 subject-years

[c]Each occurring in only 1 participant

[d]Each occurring in 1 participant except for abdominal pain (2), chest pain (3), COVID-19 (2), colon cancer (2), endometrial adenocarcinoma (2)

[e]Each occurring in 1 participant except for atrial fibrillation (2), COVID-19 (2), liver function test increased (2), squamous cell carcinoma of skin (2)

[f]Gamma-glutamyl transferase and transaminases increased

[g]Hepatoxicity (1), alanine aminotransferase increased (1), liver function test abnormal (1), endometrial adenocarcinoma (1)

[h]Liver function test abnormal (1), transaminases increased (1)

participants had prior drug-induced liver toxicity at baseline (Table 1).

TEAEs

TEAEs occurred in 55.3% of participants in the placebo group, with a slightly higher incidence observed in the fezolinetant 45 mg (62.9%) and 30 mg (65.4%) groups (Table 2). However, when controlled for exposure, the EAIR for overall TEAEs were 95.8, 75.9, and 81.4 per 100 subject-years in placebo, fezolinetant 45 mg, and fezolinetant 30 mg groups, respectively. The most frequent TEAEs in fezolinetant-treated participants included upper respiratory tract infection (7.7–8.3%), headache (6.8–8.2%), coronavirus disease 2019 (COVID-19; 5.8–6.1%), back pain (3.1–3.7%), arthralgia (2.9–3.2%), diarrhea (2.3–3.2%), urinary tract infection (2.9–3.4%), and insomnia (2.0–3.0%) (Table 3). Other TEAEs reported for ≥ 2% of the fezolinetant-treated participants included hot flash (1.7–2.2%) and weight increase (0.7–2.0%). However, weight increase was reported in 1.1% of those in the placebo group, and change from baseline to week 52 in weight in mean kg (range) was 0.15 (–18.7 to 23.6) in the fezolinetant 45 mg group, 0.23 (–22.5 to 27.0) in the fezolinetant 30 mg group, compared with 0.47 (–20.0 to 22.0) in the placebo group (Supplementary Material: Table S1).

The majority of TEAEs reported were mild or moderate in severity and occurrences were generally similar between treatment groups (Supplementary Material: Table S2). Severe TEAEs were reported for 24 participants (2.5%) in the placebo, 38 participants (3.5%) in the fezolinetant

Table 3 Frequently reported TEAEs by preferred term (safety analysis set)

Preferred term *n* (%)	Placebo (*n* = 952)	Fezolinetant 45 mg[a] (*n* = 1100)	Fezolinetant 30 mg[a] (*n* = 1103)
TEAEs ≥ 2% in any group			
Headache	73 (7.7)	90 (8.2)	75 (6.8)
Upper respiratory tract infection	78 (8.2)	85 (7.7)	91 (8.3)
COVID-19	39 (4.1)	67 (6.1)	64 (5.8)
Arthralgia	25 (2.6)	35 (3.2)	32 (2.9)
Diarrhea	23 (2.4)	35 (3.2)	25 (2.3)
Back pain	16 (1.7)	34 (3.1)	41 (3.7)
Insomnia	15 (1.6)	33 (3.0)	22 (2.0)
Urinary tract infection	22 (2.3)	32 (2.9)	37 (3.4)
ALT increased	9 (0.9)	31 (2.8)	21 (1.9)
Nasopharyngitis	24 (2.5)	27 (2.5)	31 (2.8)
Nausea	19 (2.0)	27 (2.5)	26 (2.4)
Hypertension	22 (2.3)	26 (2.4)	22 (2.0)
Fatigue	21 (2.2)	26 (2.4)	19 (1.7)
Hot flash	12 (1.3)	24 (2.2)	19 (1.7)
Blood CPK increased	3 (0.3)	23 (2.1)	15 (1.4)
Gamma-glutamyl transferase increased	12 (1.3)	16 (1.5)	26 (2.4)
Blood ALP increased	21 (2.2)	16 (1.5)	22 (2.0)
Weight increased	10 (1.1)	8 (0.7)	22 (2.0)
Additional common TEAEs			
Abdominal pain	6 (0.6)	20 (1.8)	18 (1.6)
AST increased	2 (0.2)	17 (1.5)	16 (1.5)
Blood bilirubin increased	1 (0.1)	2 (0.2)	2 (0.2)

ALP alkaline phosphatase, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *COVID-19* coronavirus disease 2019, *CPK* creatine phosphokinase, *TEAE* treatment-emergent adverse event

[a]The fezolinetant groups included participants who were re-randomized to fezolinetant after 12 weeks on placebo from SKYLIGHT 1 and 2 studies

45 mg, and 31 participants (2.8%) in the fezolinetant 30 mg groups, and included hot flash, abdominal pain, and diarrhea. Drug-related serious TEAEs occurred in 1 (0.1%) participant in the placebo group, 4 (0.4%) in the fezolinetant 45 mg group, and 2 (0.2%) in the fezolinetant 30 mg group (Table 2). A total of two deaths were reported. One participant in the 45 mg group

Table 4 TEAEs of special interest (safety analysis set)

Event of special interest, *n* (%)	Placebo (*n* = 952)	Fezolinetant 45 mg[a] (*n* = 1100)	Fezolinetant 30 mg[a] (*n* = 1103)
Liver test elevations	39 (4.1)	61 (5.5)	66 (6.0)
Uterine bleeding	33 (3.5)	30 (2.7)	36 (3.3)
Depression	19 (2.0)	21 (1.9)	27 (2.4)
Bone fractures	11 (1.2)	15 (1.4)	15 (1.4)
Endometrial hyperplasia/cancer or disordered proliferative endometrium	2 (0.2)	8 (0.7)	4 (0.4)
Wakefulness	6 (0.6)	7 (0.6)	11 (1.0)
Thrombocytopenia	2 (0.2)	2 (0.2)	5 (0.5)
Effect on memory	1 (0.1)	2 (0.2)	2 (0.2)
Abuse liability	1 (0.1)	1 (0.1)	3 (0.3)

TEAE treatment-emergent adverse event

[a]The fezolinetant groups included participants who were re-randomized to fezolinetant after 12 weeks on placebo from SKYLIGHT 1 and 2 studies

died due to multiple injuries from a motorcycle passenger accident, while a participant in the fezolinetant 30 mg group had an out-of-hospital cardiac arrest, delayed airway access, and anoxic brain injury; both deaths were considered to be not related to study treatment.

TEAEs leading to withdrawal of study treatment were similar across treatment groups, experienced by 3.9% in the placebo, 4.3% in the fezolinetant 45 mg, and 5.0% in the fezolinetant 30 mg group (Table 2). Onset of TEAEs was similar across treatment groups (Supplementary Material: Table S3).

TEAEs of special interest were reported with a similar incidence across groups. The most frequent TEAEs of special interest were liver test elevations (4.1% placebo, 5.5% fezolinetant 45 mg, and 6.0% fezolinetant 30 mg) and uterine bleeding (3.5% placebo, 2.7% fezolinetant 45 mg, and 3.3% fezolinetant 30 mg) (Table 4).

For some subgroup analyses, the interpretation was limited due to the small number of participants with selected characteristics. Overall, subgroup analyses did not reveal any populations at increased risk with fezolinetant (data not shown).

Hepatic Laboratory Assessments

Elevations in ALT and/or AST > 3× ULN occurred in 0.9% of the placebo group, 2.3% of the fezolinetant 45 mg group, and 1.5% of the fezolinetant 30 mg group (Table 5). Total bilirubin > 2× ULN occurred in 1 (0.1%) participant, in the fezolinetant 45 mg group; this participant had pre-existing Gilbert's disease, meeting study inclusion criteria. These events were typically asymptomatic. The onset of treatment-emergent elevations in ALT or AST occurred at various time points across the treatment groups, and there was no dominant pattern in the rise and fall of transaminase values. In general, hepatic transaminase levels returned to pre-treatment levels (or close to these) without sequelae with dose continuation, dose interruption, or dose discontinuation (Table 5). The majority of events in the fezolinetant-treated participants resolved on treatment. In most (*n* = 39/41) of the fezolinetant-treated participants, ALT or AST values returned to ≤ 3× ULN within approximately 1 month from the day of > 3× ULN or treatment interruption/discontinuation. ALT or AST values returned to ≤ 3× ULN in the two remaining

Table 5 Overview of hepatic laboratory assessments (safety analysis set)

Parameter and criteria, *n*/*N* (%)	Placebo (*n* = 952)	Fezolinetant 45 mg[a] (*n* = 1100)	Fezolinetant 30 mg[a] (*n* = 1103)
ALT > 3× ULN	7/917 (0.8)	23/1072 (2.1)	14/1069 (1.3)
AST > 3× ULN	4/917 (0.4)	11/1072 (1.0)	9/1069 (0.8)
ALT or AST > 3× ULN[b]	8/917 (0.9)[c]	25/1072 (2.3)	16/1069 (1.5)
Resolved on treatment[d]	6/8 (75.0)	17/25 (68.0)	12/16 (75.0)
Resolved on discontinuation[e]	2/8 (25.0)	5/25 (20.0)	3/16 (18.8)
Resolved on interruption[f]	0	3/25 (12.0)	1/16 (6.3)
ALP > 1.5× ULN	21/918 (2.3)	23/1072 (2.1)	21/1070 (2.0)
Total bilirubin > 2× ULN	0/917 (0)	1/1072 (0.1)[g]	0/1070 (0)

ALP alkaline phosphatase, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *ULN* upper limit of normal

[a]The fezolinetant groups included participants who were re-randomized to fezolinetant after 12 weeks on placebo from SKYLIGHT 1 and 2 studies

[b]Participants may have experienced one or both events

[c]1 participant was counted under placebo and fezolinetant 45 mg due to ALT or AST > 3× ULN during the 12-week placebo-controlled (on placebo) and the 40-week extension treatment periods (on fezolinetant 45 mg) – this participant returned to ≤ 3× ULN while on fezolinetant dosing

[d]ALT or AST ≤ 3× ULN during treatment period (irrespective of end of treatment status) or during follow-up period with end of treatment status = completed

[e]ALT or AST ≤ 3× ULN during follow-up period with end of treatment status = discontinued

[f]Dosing interrupted and ALT or AST ≤ 3× ULN during treatment period

[g]Participant had pre-existing Gilbert's disease

The denominator was the number of participants who had ≥ 1 non-missing value during treatment

participants (treated with fezolinetant 30 mg) after 140 and 172 days; these were adjudicated as unlikely related to treatment by the LSMP.

An independent expert LSMP-blinded review of the 48 participants with elevated transaminases (ALT or AST > 3× ULN or total bilirubin > 2× ULN) identified that 9 cases were probably related (defined as majority of data supports causal relationship to study drug; 5 in the fezolinetant 45 mg group and 4 in the fezolinetant 30 mg group). The causalities of the other events were assessed as possible (*n* = 21; 4 in the placebo group, 5 in the fezolinetant 30 mg group, and 12 in the fezolinetant 45 mg group) or unlikely (*n* = 18; 3 in the placebo group, 7 in the fezolinetant 30 mg group, and 8 in the fezolinetant 45 mg group). No specific patient characteristics predisposed these participants to elevated transaminases according to the expert LSMP.

No cases of Hy's law were reported (defined as no severe drug-induced liver injury with ALT or AST > 3× ULN and total bilirubin > 2× ULN with no elevation of alkaline phosphatase and no other etiology to explain the combination) [26].

Other Safety Considerations

Endometrial safety, determined by final biopsy diagnosis and assessed centrally, was conducted for fezolinetant-treated participants in the endometrial health set (Table 6). Endometrial hyperplasia occurred in 2 (0.6%) participants in the fezolinetant 45 mg group, 1 (0.3%) in the fezolinetant 30 mg group, and none in the placebo

Table 6 Overview of endometrial health (endometrial health set including re-randomized participants)

	Placebo (*n* = 186)	Fezolinetant 45 mg[a] (*n* = 350)	Fezolinetant 30 mg[a] (*n* = 353)
Hyperplasia, *n* (%)	0	2[b] (0.6)	1[c] (0.3)
One-sided upper limit of 95% CI[d]	1.6%	1.8%	1.3%
Disordered proliferative pattern, *n* (%)	4 (2.0)	5 (1.4)	6 (1.7)
One-sided upper limit of 95% CI[d]	4.9%	3.0%	3.3%
Malignant, *n* (%)	0	0	1 (0.3)
One-sided upper limit of 95% CI[d]	1.6%	0.9%	1.3%

CI confidence interval

[a]The fezolinetant groups included participants who were re-randomized to fezolinetant after 12 weeks on placebo from SKYLIGHT 1 and 2 studies

[b]Includes 1 participant with simple hyperplasia without atypia and 1 participant with endometrial adenocarcinoma (adverse event)

[c]1 participant with complex hyperplasia without atypia

[d]CIs are calculated using Clopper–Pearson exact method for binomial proportions

group. Endometrial malignancy occurred in none in the fezolinetant 45 mg group, in 1 (0.3%) participant in the fezolinetant 30 mg group, and none in the placebo group. These values were within US Food and Drug Administration (FDA) pre-specified limits of ≤ 1% with an upper limit of 1-sided 95% CI that does not exceed 4% [27].

Endometrial thickness, measured by TVU during the assessment period, was assessed in the safety analysis set. Endometrial thickness was similar in all three treatment groups. Mean change (SD) [range] from baseline to week 52 was – 0.17 mm (2.35) [– 9.1, 10.5] with placebo (*n* = 316), – 0.24 mm (2.23) [– 16.5, 9.1] with fezolinetant 45 mg (*n* = 582), and – 0.24 (2.11) [– 12.7 to 8.0] with fezolinetant 30 mg (*n* = 576). A disordered endometrial proliferative pattern, determined by the final biopsy diagnosis, was observed in 5 (1.4%) participants in the fezolinetant 45 mg group (upper limit of one-sided 95% CI of 3.0%), 6 (1.7%) participants in the fezolinetant 30 mg group (upper limit of one-sided 95% CI of 3.3%), and 4 (2.0%) in the placebo group (upper limit of one-sided 95% CI of 4.9%) (Table 6).

A small number of benign and non-benign neoplasms were reported in the pooled safety analysis set. Benign neoplasms were reported in 10 (1.1%) participants in the placebo group, 15 (1.4%) in the fezolinetant 45 mg group, and 13 (1.2%) in the fezolinetant 30 mg group. The corresponding EAIR for benign neoplasms were similar across the groups: 1.8, 1.6, and 1.5 per 100 subject-years in the placebo, fezolinetant 45 mg, and fezolinetant 30 mg groups, respectively. In total, 11 non-benign neoplasms were reported with fezolinetant 45 mg (1.0%; 1.2 per 100 subject-years), compared with 6 with fezolinetant 30 mg (0.5%; 0.7 per 100 subject-years), and 1 with placebo (0.1%; 0.2 per 100 subject-years). No signal of increased risk for benign or non-benign neoplasms overall was observed in the pooled population (Supplementary Material: Table S4).

DISCUSSION

The results of this pooled analysis confirm the safety and tolerability of fezolinetant treatment over 52 weeks in nearly 3000 women with VMS due to menopause. The incidence of drug-related serious TEAEs and drug-related TEAEs leading to withdrawal were low, and elevations in liver transaminases were infrequent and generally

asymptomatic. Overall, fezolinetant demonstrated a favorable safety and tolerability profile over 52 weeks with results consistent with the previously reported individual study findings [22–24].

No new safety concerns were identified in this pooled analysis, which includes 52-week data from all three randomized phase 3 studies. The majority of TEAEs were not drug-related, while the most common events were upper respiratory tract infection, headache, and COVID-19, and a similar frequency was observed across the three treatment arms. Similarly, TEAEs of special interest (including liver test elevations, uterine bleeding, and depression) were infrequently reported in both fezolinetant- and placebo-treated patients. Other adverse events observed with fezolinetant treatment include abdominal pain, diarrhea, insomnia, back pain, hot flash, and hepatic transaminase elevation.

Liver-related health is an important consideration in menopausal women: several factors including age, NAFLD, hormonal factors, BMI, concomitant medications, and alcohol consumption are reported to be associated with liver disease [28–30]. The present pooled analysis showed elevations in ALT and/or AST > 3× ULN occurred in 2.3% of participants treated with fezolinetant 45 mg and 1.5% of the fezolinetant 30 mg group, compared with 0.9% of those treated with placebo, while one (0.1%) participant (in the fezolinetant 45 mg group, with pre-existing Gilbert's disease) had elevated total bilirubin > 2× ULN. Overall, there was no evidence of liver function impairment, including no Hy's law cases observed, and hepatic transaminase elevations were generally transient and reversed on treatment or with interruption/discontinuation. The independent review of participants with elevated liver function markers by the LSMP concluded that cases appear to be rare in fezolinetant-treated patients and no specific predisposing characteristics were identified (such as BMI, history of NAFLD or NASH, age, concomitant medications, or race/ethnicity). Overall, this pooled analysis indicated that fezolinetant did not reproduce the signals of potential liver toxicity previously reported with another NK3R antagonist MLE4901 [31] and supports that there are no drug-class liver safety effects [32].

The FDA draft guidance on hormonal products to treat VMS recommends that, for approval, clinical trials demonstrate an endometrial hyperplasia rate of ≤ 1%, with an upper bound not to exceed 4% of the one-sided 95% CI, with this recommendation also applicable for nonhormonal products [27]. After 52 weeks of treatment, the pooled analysis reported a single case of endometrial hyperplasia (0.3%) in the fezolinetant 30 mg group, 2 cases (0.6%) in the fezolinetant 45 mg group, and a single case of endometrial malignancy (0.3%) in the fezolinetant 30 mg group; these results were well within the FDA criterion for endometrial safety. These data, combined with that of TVU, indicate that fezolinetant had no clinically relevant effect on the endometrium and provides an important nonhormonal treatment.

Epidemiology studies confirm that certain malignancies, e.g., breast, endometrial, skin, colon, etc., occur in women of mid-life age [33, 34]. This pooled analysis of SKYLIGHT 1, 2, and 4 reported a similar rate of benign neoplasms in the fezolinetant- and placebo-treated participants, but a numeric imbalance was identified for non-benign neoplasms in SKYLIGHT 4 [33]. Since this was not previously seen in fezolinetant studies, a post hoc in-depth, comprehensive analysis of phase 2 and phase 3 clinical data from the fezolinetant development program was performed. This analysis was combined with a comprehensive assessment of key characteristics of carcinogens [35], an evaluation of fezolinetant structural properties and non-clinical data, and an epidemiologic literature review. Based on the in-depth clinical review of each non-benign neoplasm presentation, a drug effect for increased risk was not supported given short latency periods to diagnosis (in most cases within 3–6 months), tumor type heterogeneity, prior neoplastic/risk factor history, and presence of alternative baseline etiologies (such as a pre-existing condition at study entry) [36, 37]. No evidence of genotoxicity or carcinogenicity was observed during the fezolinetant preclinical investigations, and there is no known agent that could be singularly responsible for the infrequent and diverse pathophysiologies of the neoplasms that were reported in the fezolinetant clinical programs. Furthermore, a clinical

review performed by the FDA found there were insufficient data to support an increased risk of malignancy in patients who received fezolinetant and the incidence rate of malignancy TEAEs was within the normal background rate of cancer for the age group of this population. Additionally, the placebo arm had lower than expected rate of malignancy as compared to the background rate [38]. In support of these findings, the European Medicines Agency stated "the noted imbalance of serious events of malignancy cases of diverse origin in the fezolinetant groups as compared to the placebo groups are considered a chance finding" and "inclusion in the Summary of Product Characteristics of fezolinetant is not needed" [39]. In addition, no plausible mechanism exists for NK3R antagonism in neoplasms [40]. Importantly, although tachykinin agonism could be involved in neoplastic development, antagonism has been considered as a potential antineoplastic target [37, 41].

A key strength of the pre-specified pooled SKYLIGHT 1, 2, and 4 analysis was that safety and tolerability data were attained from a large number of participants who were treated for up to 52 weeks. Other strengths include the range of relevant safety endpoints assessed and the inclusion of participants with broad eligibility criteria at baseline, such as BMI ≤ 38, prior menopausal HT, hysterectomy history, oophorectomy history, current smoker, current alcohol use, NAFLD, NASH, spontaneous amenorrhea for ≥ 12 months, diabetes mellitus, and Gilbert's syndrome with elevated total bilirubin.

Although all three trials included similar placebo-controlled trial designs, a potential limitation is that two of the trials included a placebo-controlled period of only 12 weeks followed by a 40-week (non-placebo–controlled) active treatment extension period. However, this limitation was compensated for by the 52-week placebo-controlled SKYLIGHT 4 study. Additionally, in some patients, VMS symptoms were reported to worsen relative to the pre-treatment state, regardless of treatment arm. It is difficult to differentiate whether worsening hot flashes were caused by menopause or other factors such as a period of missed doses, environmental considerations, loss of effect after last dose, or by lack of efficacy with treatment. If hot flash was reported by the patient or researcher, it was captured in the data as an adverse event.

CONCLUSION

This pooled analysis of SKYLIGHT 1, 2, and 4 represents a comprehensive assessment of safety and tolerability outcomes in women with moderate to severe VMS due to menopause treated with fezolinetant over 52 weeks. The incidence of drug-related serious TEAEs and associated treatment withdrawals was low. In addition, elevations in liver transaminases were infrequent and they were typically asymptomatic, transient, and reversed on treatment or with interruption/discontinuation; there was no evidence of liver function impairment. The imbalance in neoplasms was analyzed, and no increased risk was demonstrated based on the total evidence.

Overall, these results confirm the safety and tolerability and support the use of fezolinetant 45 mg as an important nonhormonal treatment option for women with moderate to severe VMS due to menopause.

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

Declarations

Conflict of Interest. RK has received consulting/advisory board fees from Astellas, Pfizer, and Mayne, participated in the data monitoring committee for Astellas (ended), received speaker fees from Pfizer and Astellas, and acted as Medical Advisor for Carrot Fertility. AC acted as former President of the European Menopause and Andropause Society and consulted for Astellas, Theramex, and Viatris. REN received grants from Fidia, consulting fees from Astellas, Besins, Bayer, Exeltis, Fidia, Freya, HRA, Theramex, and Vichy Laboratories, honoraria for lectures from Abbott, Bayer, Exeltis, Novo Nordisk, Organon, Shionogi, Theramex, and Viatris, was a researcher for Fidia, Merck, and Shionogi, and is President Elect of the International Menopause Society. MLE, SM, XW, and FDO are employees of Astellas.

Ethical Approval. SKYLIGHT 1, 2, and 4 were conducted in accordance with 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 at each site before data collection. Written informed consent was obtained from all participants before any study-related procedures.

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