Fezolinetant (VEOZA™) as a Non-hormonal Treatment for Moderate-to-Severe Vasomotor Symptoms in Postmenopausal Women: A Systematic Literature Review and Meta-Analysis

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INTRODUCTION

- Moderate-to-severe vasomotor symptoms (**VMS**) affect approximately 11–46% of women aged over 40 years, with a median total symptom duration of about 7.4 years[1]
- **Fezolinetant** is an oral, nonhormonal neurokinin 3 (NK3) receptor antagonist that offers a novel therapeutic approach for managing moderate-to-severe VMS. It's 45 mg once daily dose has been approved in the United States, Europe, and Australia[2]
- This systematic literature review (SLR) and meta-analysis aimed to evaluate the efficacy and safety of fezolinetant 30 mg and 45 mg versus placebo in postmenopausal women with moderate-to-severe VMS

METHOD

- A systematic search was conducted in PubMed, Cochrane Library, and clinical trial registries (ClinicalTrials.gov, WHO ICTRP, and ANZCTR) from inception to May 2025
- Meta-analyses were performed for fezolinetant 30 mg and 45 mg doses to assess changes from baseline in the frequency and severity of VMS
- A meta-regression analysis explored whether treatment effects differed between trial populations (menopausal hormone therapy [MHT]–unsuitable population versus overall population)
- **Table 1** summarizes the eligibility criteria applied for study selection

Table 1. Eligibility Criteria

Component	Description
Population	Patient with moderate-to-severe vasomotor symptoms associated with confirmed menopausal status who are unsuitable for menopausal hormone therapy
Intervention	Fezolinetant
Comparator	Placebo
Outcomes	**Efficacy outcomes:** • Mean change in the severity of moderate-to-severe vasomotor symptoms • Mean change in the frequency of moderate-to-severe vasomotor symptoms **Safety outcomes:** • Treatment-emergent adverse events
Study design	Randomized controlled trials
Language	English only publications

RESULTS

- The SLR identified 208 records, of which **36 publications** corresponding to five randomized controlled trials (RCTs) [DAYLIGHT, MOONLIGHT-1, SKYLIGHT-1, SKYLIGHT-2, and SKYLIGHT-4] met the inclusion criteria
- **Table 2** summarizes the characteristics of the included trials
- Across MOONLIGHT-1, SKYLIGHT-1, and SKYLIGHT-2, fezolinetant 30 mg significantly reduced the frequency of moderate-to-severe VMS compared with placebo (pooled MD = −1.50 episodes/day; 95% CI: −2.11 to −0.88; I^2 = 68%) **(Figure 1)**
- The severity of VMS also improved from baseline versus placebo (pooled MD = −0.12; 95% CI: −0.18 to −0.07; I^2 = 0%) **(Figure 2)**

Figure 1. Frequency of moderate-to-severe VMS for 30 mg fezolinetant

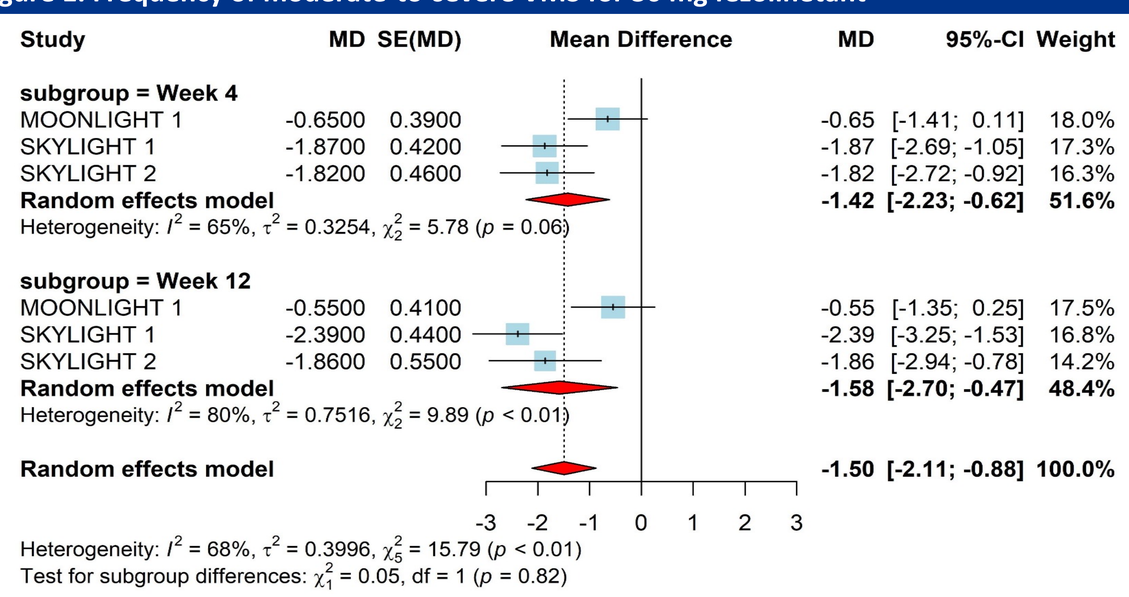
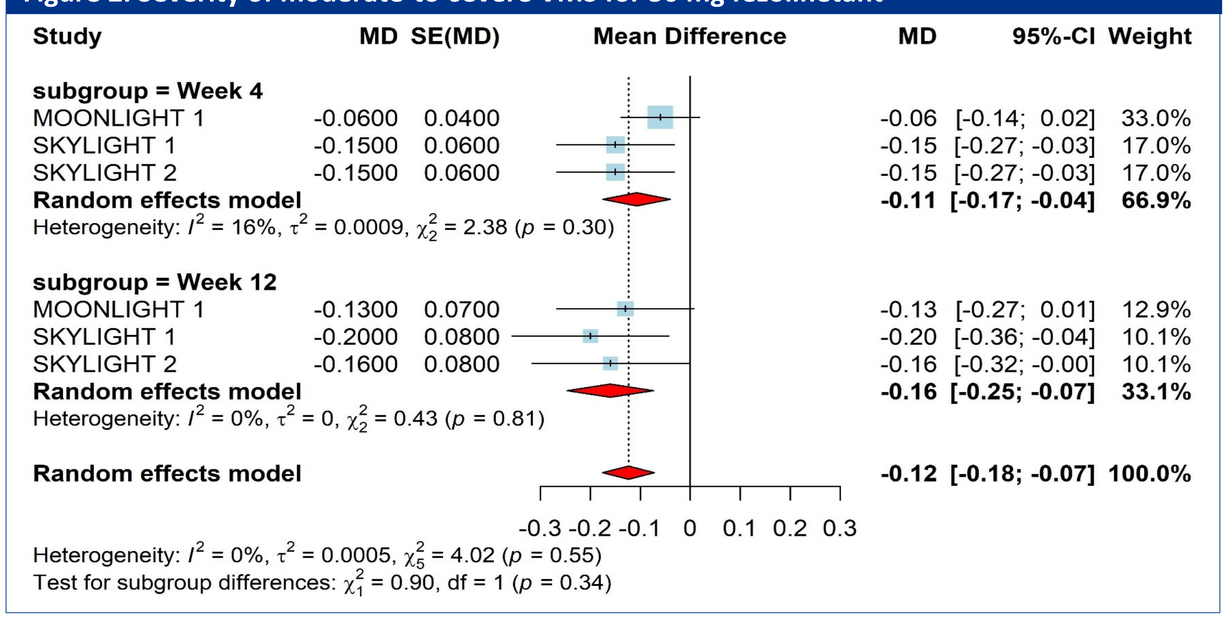


Figure 2. Severity of moderate-to-severe VMS for 30 mg fezolinetant



Abbreviations: CI, confidence interval; MD, mean difference; SE, standard error; VMS, vasomotor symptoms.

FUNDING This study did not receive any funding and the authors declare no conflicts of interest

Table 2. Study Characteristics of the Included Studies

Study name	Treatment arm (N)	Age in years, mean (SD)	Population description	Outcome assessed
DAYLIGHT[1]	Placebo (226) Fezolinetant 45 mg (226)	54.1 (4.6) 54.9 (4.8)	Moderate-severe VMS and considered unsuitable for MHT	**P:** mean change in daily frequency of moderate-to-severe VMS **S:** mean change in symptom severity, sleep disturbance and safety
MOONLIGHT-1[2]	Placebo (151) Fezolinetant 45 mg (150)	54.8 (4.4) 54.7 (4.5)	Postmenopausal women with moderate-to-severe VMS, seeking treatment for VMS	**CP:** mean changes in the daily frequency and severity of VMS at weeks 4 & 12
SKYLIGHT-1[3]	Placebo (175) Fezolinetant 30 mg (174) Fezolinetant 45 mg (173)	54.7 (4.8) 54.2 (4.9) 54.2 (5.1)	Moderate-to-severe VMS associated with menopause	**CP:** mean changes in the frequency and severity of VMS from baseline to weeks 4 & 12
SKYLIGHT-2[4]	Placebo (167) Fezolinetant 30 mg (166) Fezolinetant 45 mg (167)	54.7 (4.6) 53.9 (4.9) 54.3 (5.4)	Moderate-to-severe VMS associated with menopause	**CP:** mean changes in the daily frequency and severity of moderate-to-severe VMS from baseline to weeks 4 & 12
SKYLIGHT-4[5]	Placebo (610) Fezolinetant 30 mg (611) Fezolinetant 45 mg (609)	54.9 (4.8) 54.7 (4.7) 54.7 (4.7)	Female aged ≥40 and ≤65 years seeking treatment for VMS associated with menopause	**P:** TEAE, percentage of participants with endometrial hyperplasia & percentage with endometrial malignancy **S:** change in BMD and trabecular bone score

Abbreviations: BMD, bone mineral density; CP, co-primary endpoints; HT, hormone therapy; P, primary endpoint; S, secondary endpoint; TEAE, treatment-emergent adverse events; VMS, vasomotor symptoms.

- At the 45 mg dose, across DAYLIGHT, SKYLIGHT-1, and SKYLIGHT-2, fezolinetant showed larger reductions in VMS frequency (pooled MD = −2.25 episodes/day; 95% CI: −2.74 to −1.77; I^2 = 0%) **(Figure 3)** and in VMS severity (pooled MD = −0.29 points; 95% CI: −0.39 to −0.18; I^2 = 20%) **(Figure 4)**
- Adverse-event rates were comparable between fezolinetant and placebo across all studies, with no dose-related discontinuations observed

Figure 3. Frequency of moderate-to-severe VMS for 45 mg fezolinetant

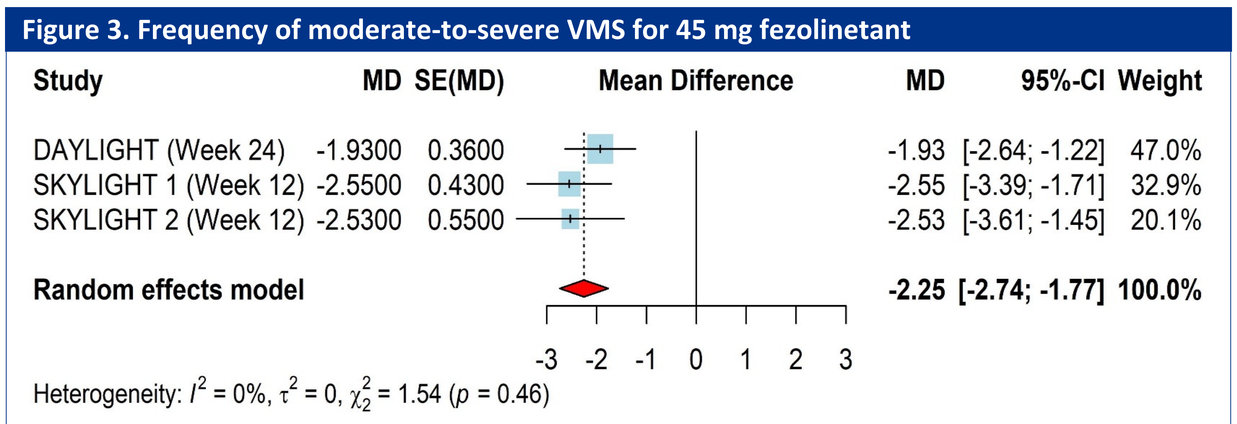
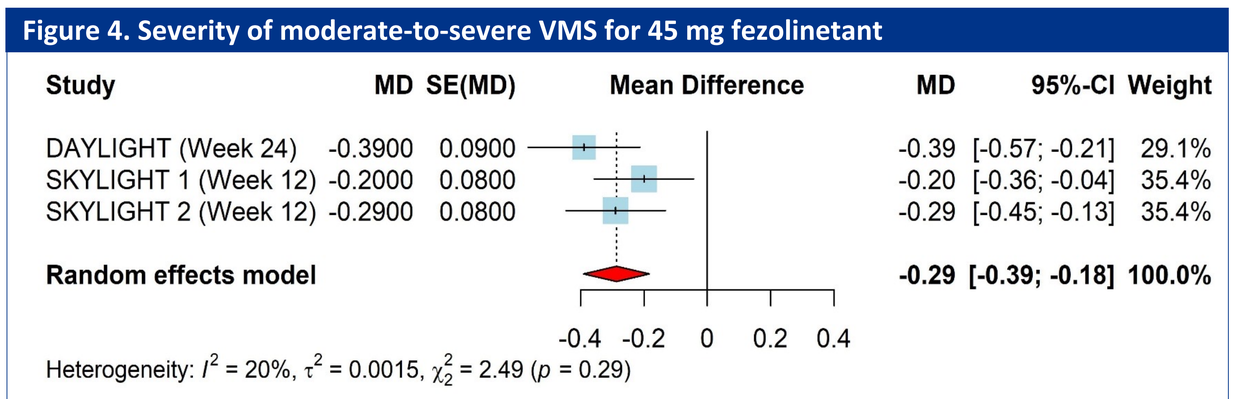


Figure 4. Severity of moderate-to-severe VMS for 45 mg fezolinetant



Abbreviations: CI, confidence interval; MD, mean difference; SE, standard error; VMS, vasomotor symptoms.

- Meta-regression analyses found no significant effect modification by trial population (MHT-unsuitable vs. overall) for either VMS frequency (p=0.215, **Figures 5**) or VMS severity (p=0.173, **Figures 6**)

Figure 5. Bubble plot: Frequency of moderate-to-severe VMS for 45mg fezolinetant

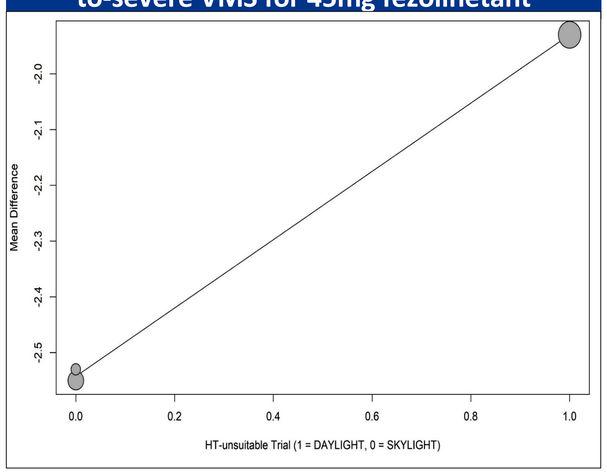
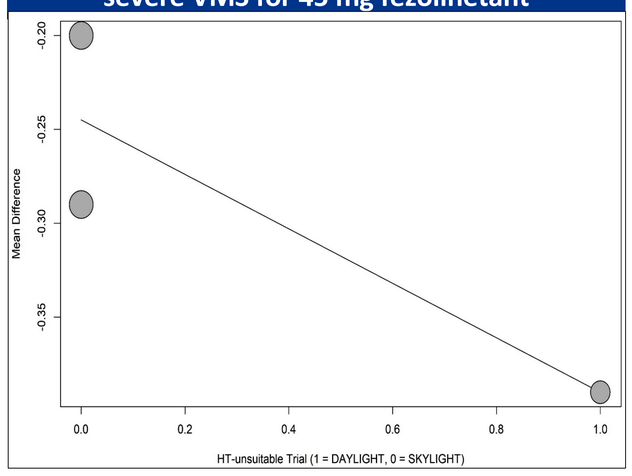


Figure 6. Bubble plot: Severity of moderate-to-severe VMS for 45 mg fezolinetant



Abbreviations: HT, hormone therapy; VMS, vasomotor symptoms.

CONCLUSIONS

Fezolinetant provides dose-dependent reductions in VMS frequency and severity. The 45 mg dose exceeded the accepted clinical benefit threshold of ≥2 VMS/day reduction, indicating a clinically meaningful benefit. These findings support fezolinetant 45 mg as an effective and well-tolerated non-hormonal treatment option for postmenopausal women, including those unsuitable for MHT

Poster presented at ISPOR EUROPE 2025, Glasgow, Scotland (9-12 Nov 2025)

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