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INTRODUCTION

- Vasomotor symptoms (VMS), characterised by hot flashes and/or night sweats, affect many women during menopausal transition¹
- Severe VMS adversely affect sleep, concentration, mood, energy and sexual activity²
- Fezolinetant, a nonhormonal selective neurokinin 3 receptor antagonist that moderates neuronal activity in the hypothalamic thermoregulatory centre, is in development for the treatment of VMS associated with menopause
- Objective: to evaluate efficacy and safety of fezolinetant versus placebo on frequency and severity of moderate-to-severe VMS associated with menopause

METHODS

Study design for SKYLIGHT 2 (NCT04003142)

- Double-blind, placebo-controlled, multicentre Phase 3 study of women aged 40–65 years with moderate-to-severe VMS associated with menopause (minimum average 7 moderate-to-severe hot flashes/day; **Figure 1**)
- Those completing 12 weeks of treatment continued their fezolinetant dose; those on placebo were re-randomised to fezolinetant 30 mg or 45 mg/day

Endpoints

- Co-primary efficacy endpoints: mean change from baseline to weeks 4 and 12 in frequency and severity of moderate-to-severe VMS
- Secondary endpoints: mean change in frequency and severity of moderate and severe VMS each week from baseline to week 12; mean change in Patient-Reported Outcomes Measurement Information System Sleep Disturbance–Short Form 8b³ (PROMIS SD SF 8b) Total Score from baseline to week 12
- Treatment-emergent adverse events (TEAEs) assessed safety and tolerability

Statistical analysis

- For each co-primary efficacy endpoint, a mixed model repeated measures analysis of covariance model was used with change from baseline as the dependent variable and treatment group, week and smoking status (current vs former/never) as factors, with baseline measurement and baseline weight as covariates, as well as an interaction of treatment by week and an interaction of baseline measurement by week
- Statistical significance for the 4 co-primary efficacy endpoints was determined by the Hochberg method

RESULTS

Study population

- 500 women were randomised and took ≥1 dose: placebo, n=167; fezolinetant 30 mg, n=166; fezolinetant 45 mg, n=167
- Details of baseline characteristics are summarised in **Table 1**

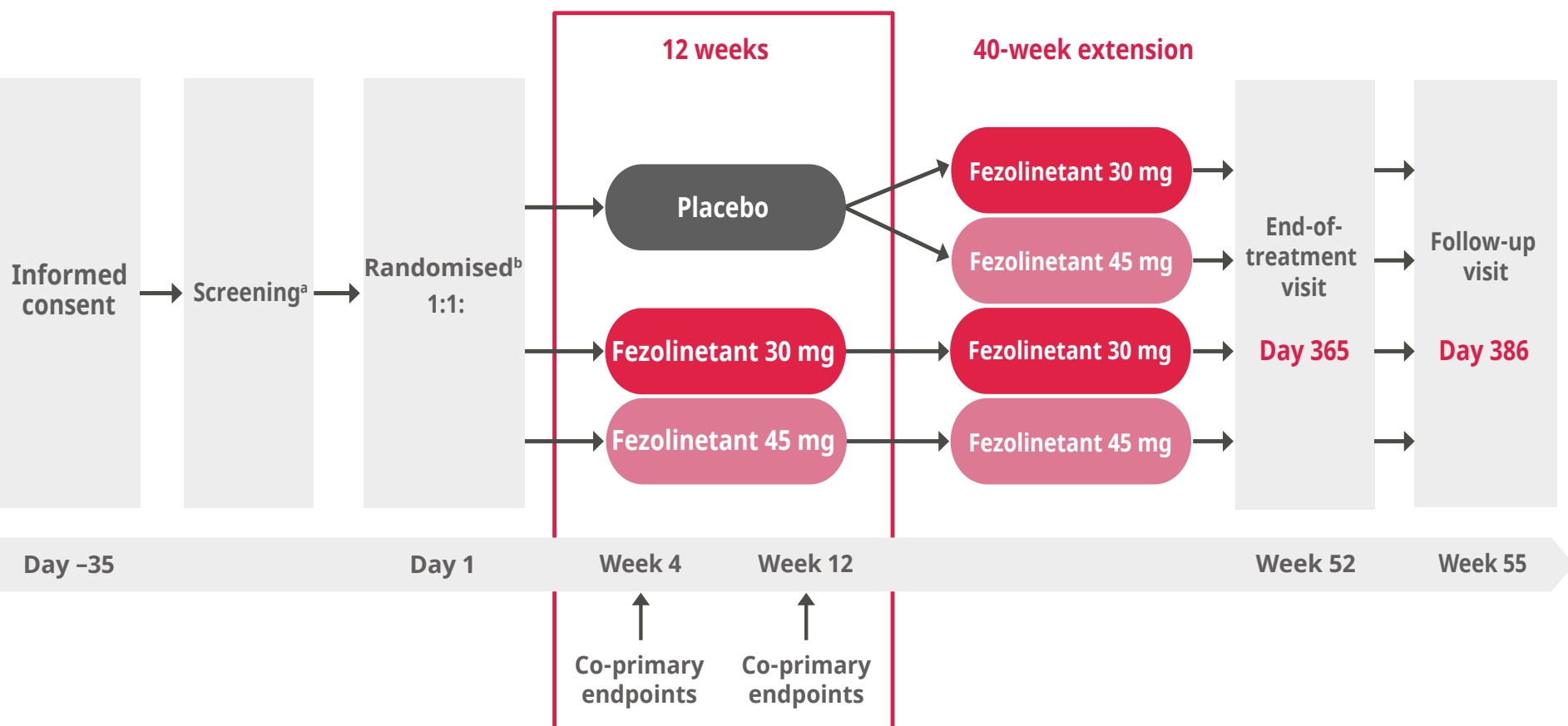
Efficacy assessments

- Both fezolinetant doses met statistical significance in reducing VMS frequency and severity at weeks 4 and 12 versus placebo (**Figures 2 and 3**)
 - Improvements were seen as early as week 1 and maintained over 12 weeks (**Figure 4**)
- Reduction in PROMIS SD SF 8b Total Score versus placebo at week 12 was statistically significant for fezolinetant 45 mg, but not 30 mg (**Figure 5**)

Safety assessments

- A summary of the safety data is shown in **Table 2**
- Headache was the most common TEAE in the fezolinetant groups
- Of 500 women, 6 had alanine aminotransferase (ALT) values >3 times upper limit of normal (ULN); 2 fezolinetant 30 mg, 3 fezolinetant 45 mg, 1 placebo. One woman on fezolinetant 30 mg had an ALT result >5 times ULN. Aspartate aminotransferase values >3 times ULN occurred in 1 fezolinetant 30 mg and 1 placebo participant
- No elevations were associated with evidence of liver functional impairment (increased bilirubin or international normalised ratio) or liver-associated symptoms

Figure 1. Study design



FDA, US Food and Drug Administration; VMS, vasomotor symptoms
^aVMS data were collected using an electronic hot flash diary. Women were provided with a reference guide within the diary, which included definitions for mild, moderate and severe VMS, according to FDA guidance: mild, sensation of heat without sweating; moderate, sensation of heat with sweating, able to continue activity; severe, sensation of heat with sweating, causing cessation of activity
^bSmoking status was a randomisation stratification factor

Table 1. Demographic and baseline characteristics

	Placebo (n=167)	Fezolinetant 30 mg (n=166)	Fezolinetant 45 mg (n=167)	Total (N=500)
White, n (%)	134 (80.2)	131 (78.9)	132 (79.0)	397 (79.4)
Black/African American, n (%)	31 (18.6)	35 (21.1)	33 (19.8)	99 (19.8)
American Indian/Alaska Native, Asian, Other ^a , n (%)	2 (1.2)	0	2 (1.2)	4 (0.8)
Hispanic or Latina, n (%)	32 (19.3) ^b	34 (20.5)	41 (24.6)	107 (21.4) ^b
Age, mean (SD), y	54.7 (4.6)	53.9 (4.9)	54.3 (5.4)	54.3 (5.0)
BMI, mean (SD), kg/m ²	28.16 (4.99)	27.94 (4.69)	27.91 (4.35)	28.00 (4.68)
Time since onset of HF, mean (SD), mo	81.9 (73.3)	76.2 (74.4)	81.7 (74.1)	80.0 (73.9)
Hysterectomy, n (%)	51 (30.5)	53 (31.9)	56 (33.5)	160 (32.0)

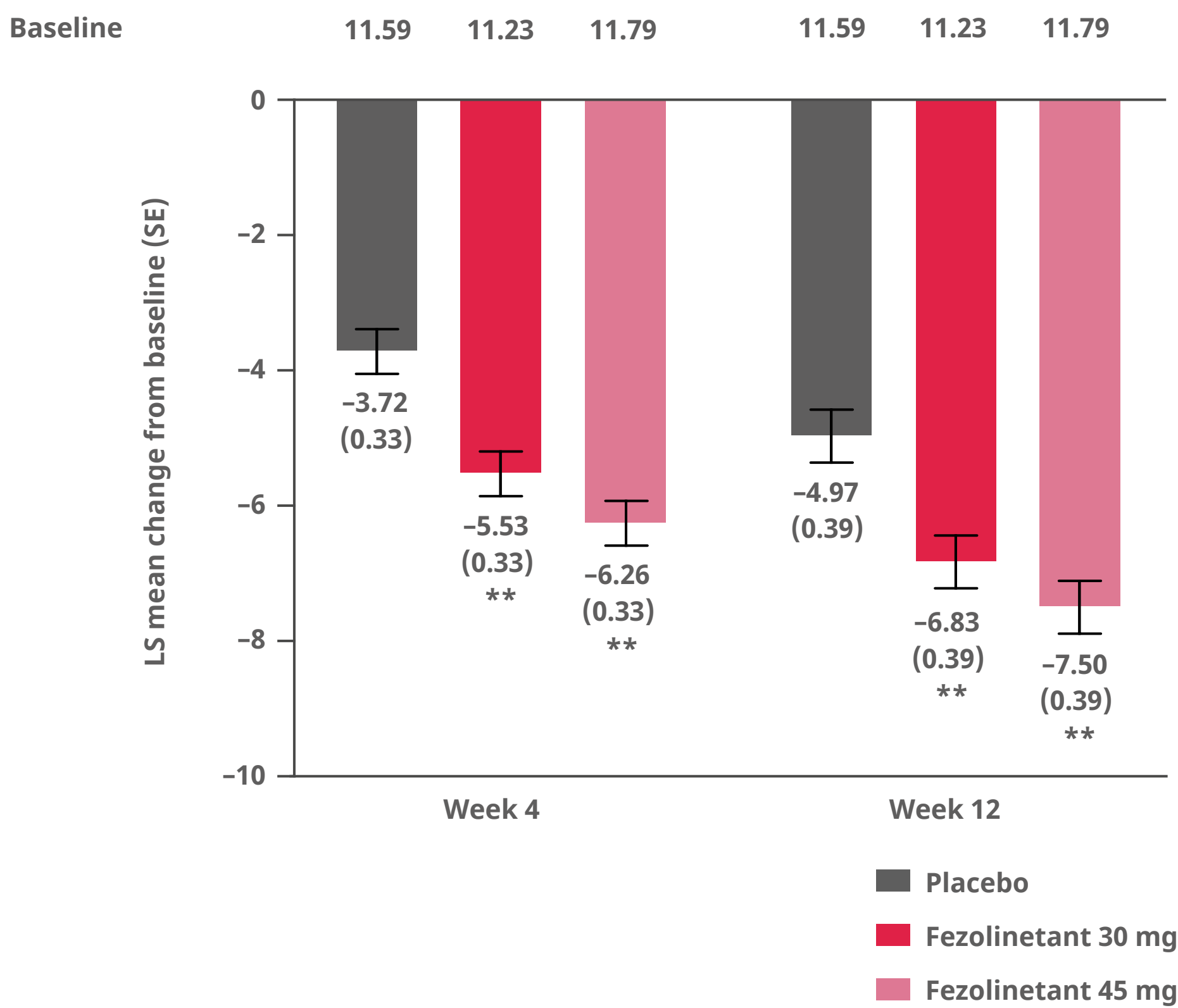
BMI, body mass index; HF, hot flash; SD, standard deviation
^aMore than 1 race
^bMissing=1

Table 2. Overview of adverse events

TEAE, n (%)	Placebo (n=167)	Fezolinetant 30 mg (n=166)	Fezolinetant 45 mg (n=167)
TEAE	54 (32.3)	67 (40.4)	60 (35.9)
Drug-related TEAE	11 (6.6)	24 (14.5)	25 (15.0)
Serious TEAE ^a	0	3 (1.8)	2 (1.2)
Drug-related serious TEAE	0	0	0
TEAE leading to permanent discontinuation of study drug	1 (0.6)	2 (1.2)	5 (3.0) ^b
Drug-related TEAE leading to permanent discontinuation of study drug	0	1 (0.6)	5 (3.0)
TEAE by preferred term (≥2% for any group)			
Upper respiratory tract infection	7 (4.2)	5 (3.0)	5 (3.0)
Headache	4 (2.4)	5 (3.0)	6 (3.6)
Dry mouth	0	4 (2.4)	4 (2.4)
Arthralgia	1 (0.6)	5 (3.0)	1 (0.6)
Diarrhoea	4 (2.4)	1 (0.6)	2 (1.2)
Nasopharyngitis	4 (2.4)	3 (1.8)	0
Nausea	0	3 (1.8)	4 (2.4)
Weight increased	1 (0.6)	5 (3.0)	1 (0.6)

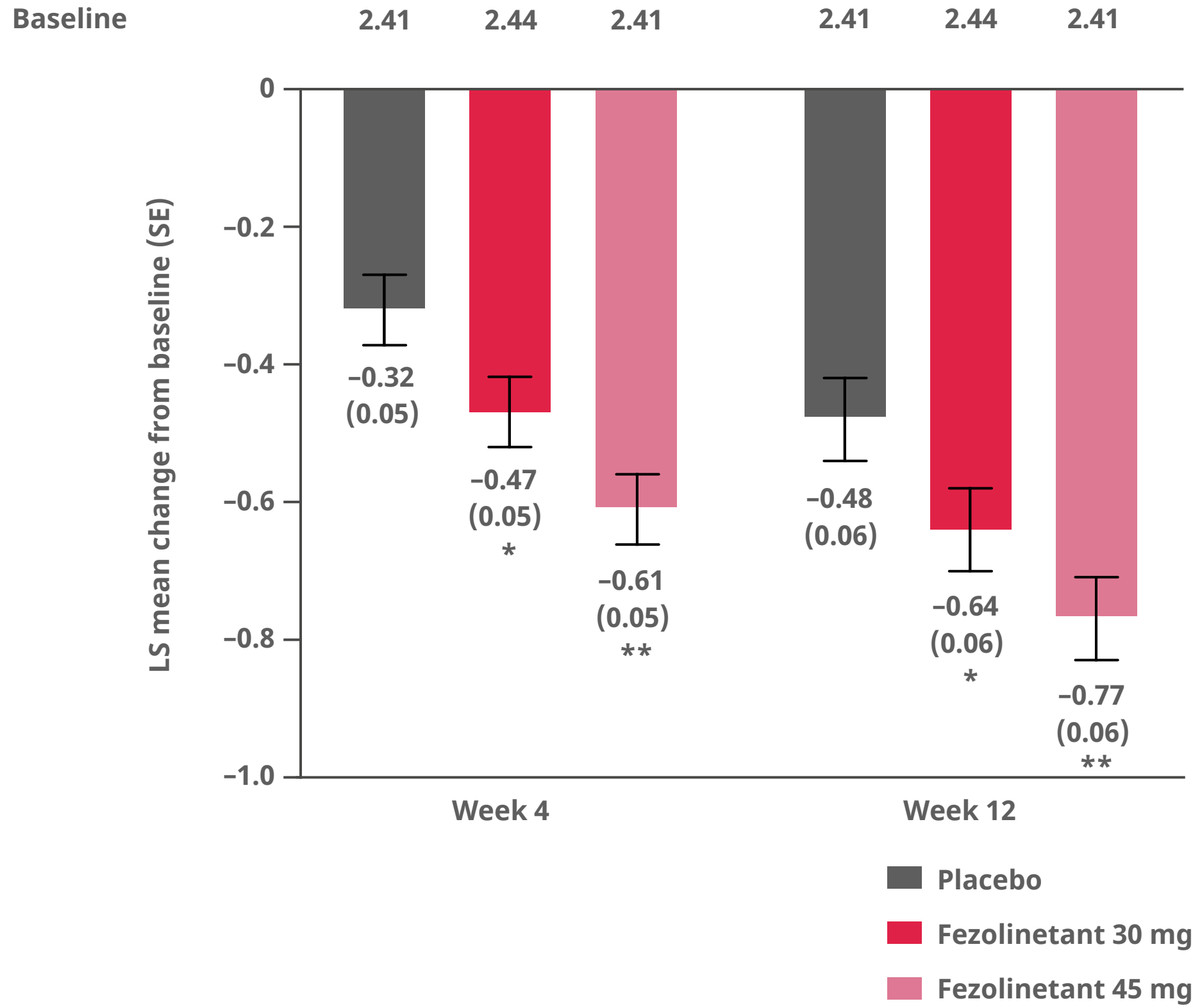
TEAE, treatment-emergent adverse event
^aNo serious TEAEs of liver enzyme elevation were reported
^bOne participant had alanine aminotransferase increased

Figure 2. Change from baseline in mean frequency of VMS



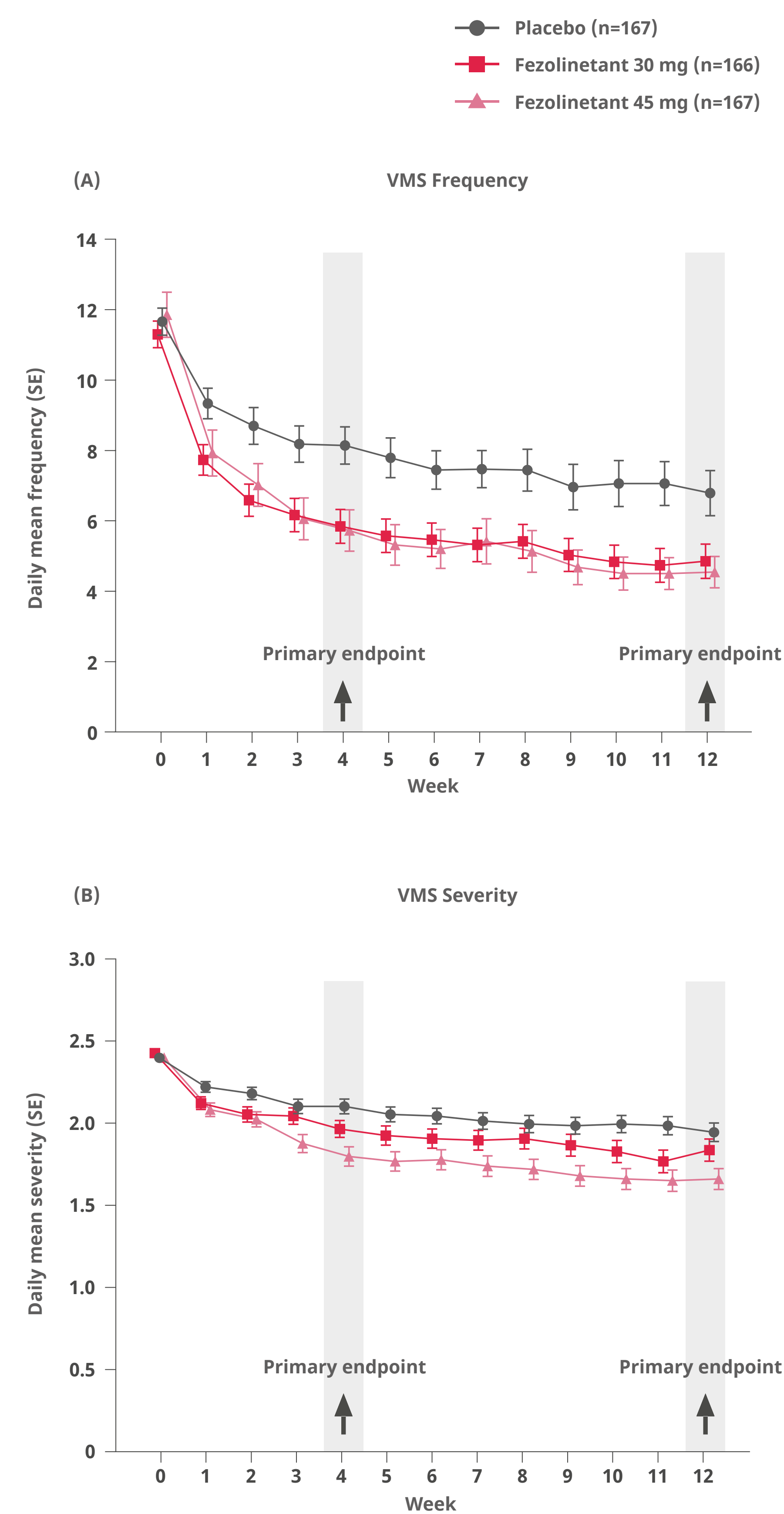
LS, least squares; SE, standard error; VMS, vasomotor symptoms
**Nominal p<0.001. Statistically significant with the Hochberg method

Figure 3. Change from baseline in mean severity of VMS



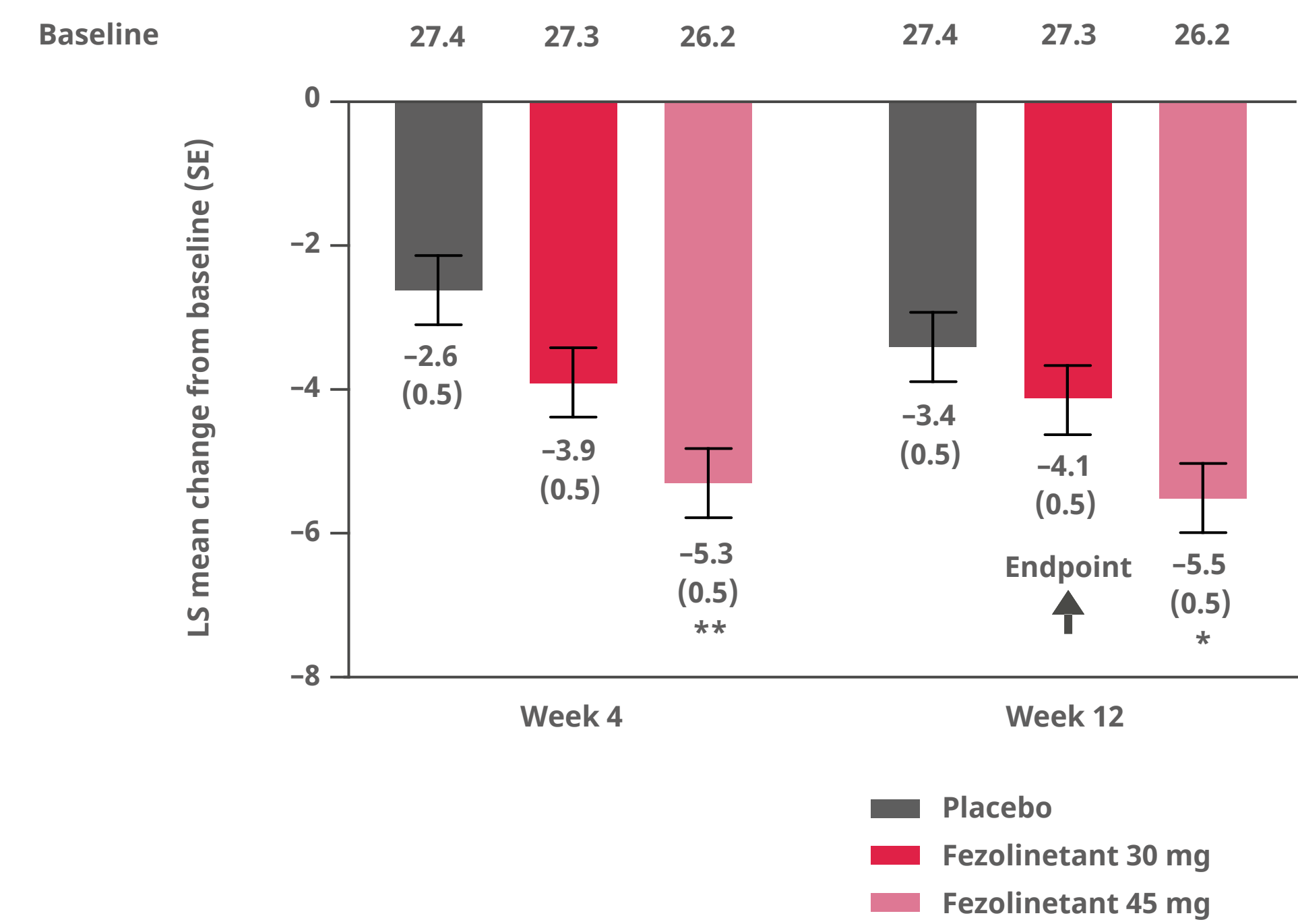
LS, least squares; SE, standard error; VMS, vasomotor symptoms
*Nominal p<0.05; **p<0.001. Statistically significant with the Hochberg method

Figure 4. Mean frequency and severity of moderate and severe VMS over time



SE, standard error; VMS, vasomotor symptoms

Figure 5. Change from baseline in PROMIS SD SF 8b Total Score



LS, least squares; PROMIS SD SF 8b, Patient-Reported Outcomes Measurement Information System Sleep Disturbance–Short Form 8b; SE, standard error
*p<0.05; **p<0.001

CONCLUSIONS

- Fezolinetant 30 mg and 45 mg once daily were efficacious and well tolerated for the treatment of moderate-to-severe VMS associated with menopause
- Full safety results will be obtained on completion of the fezolinetant Phase 3 programme

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CONFLICT OF INTEREST

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