Fezolinetant for Treatment of Moderate-to-severe Vasomotor Symptoms Associated with Menopause: Results from a 52-week Study (Skylight 2)

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Background: SKYLIGHT 2 (NCT04003142) investigated safety and efficacy of fezolinetant (a neurokinin-3 receptor antagonist) on frequency and severity of moderate-to-severe vasomotor symptoms (VMS) and sleep disturbance. In this analysis, persistence of fezolinetant efficacy was investigated over 52 weeks.

Methods: This double-blind Phase 3 study randomized women aged ≥40–65 years with moderate-to-severe VMS associated with menopause (average of ≥7 hot flashes/day) to once-daily placebo or fezolinetant 30mg or 45mg for 12 weeks. Women completing 12 weeks entered an extension period, with those on placebo re-randomized to fezolinetant 30mg or 45mg (placebo/fezolinetant), and those originally on fezolinetant remaining on their dose for an additional 40-weeks. Fezolinetant efficacy was evaluated vs placebo for 12-weeks through change in VMS frequency, VMS severity, and Patient-reported Outcomes Measurement Information System Sleep Disturbance–Short Form 8b (PROMIS) Total Score. Persistence of efficacy for fezolinetant was evaluated descriptively (without statistical comparisons) over the extension period.

Results: The analysis comprised 484 women (fezolinetant 30mg n=166, fezolinetant 45mg n=167, placebo/fezolinetant 30mg n=76, placebo/fezolinetant 45mg n=75). Improvement in VMS frequency and severity observed through week 12 (statistically significant differences vs placebo) was maintained throughout the 52-week total study period for those receiving fezolinetant. Fezolinetant demonstrated further reductions in VMS frequency and severity from baseline to beyond week 12. For VMS frequency, there was a least squares (LS) mean (SE) baseline-to-week 12 reduction of –6.83 (0.39) VMS/day for fezolinetant 30mg and –7.50 (0.39) for 45mg, and a mean (SD) baseline-to-week 52 reduction of –8.03 (4.53) for fezolinetant 30mg and –8.48 (3.98) for 45mg. For VMS severity, LS mean (SE) baseline-to-week 12 reduction was –0.64 (0.06) for 30mg and –0.77 (0.06) for 45mg, and mean (SD) baseline-to-week 52 reduction was –0.83 (0.82) for fezolinetant 30mg, and –0.95 (0.78) for 45mg. Women re-randomized from placebo to fezolinetant experienced a reduction in frequency and severity of VMS consistent with that in women receiving fezolinetant throughout the study. Fezolinetant also reduced PROMIS-assessed sleep disturbance, with a LS mean (SE) baseline-to-week 12 reduction of –4.1 (0.5) for fezolinetant 30mg and –5.5 (0.5) for 45mg (statistically significant difference vs placebo for fezolinetant 45mg) and a mean (SD) baseline-to-week 52 reduction of – 6.3 (7.3) for fezolinetant 30mg and –5.7 (7.9) for 45mg. The safety profile observed for the 40-week extension period was consistent with that of the 12-week placebo-controlled period.

Conclusion: Fezolinetant 30mg and 45mg once daily were efficacious for treatment of moderate-to-severe VMS associated with menopause. Efficacy was persistent and reductions in VMS frequency were maintained during the extension period, at levels consistent with weeks 1 through 12. Fezolinetant 45mg improved sleep at week 12 and improvement was maintained through the active treatment extension period. No safety signals of concern were apparent for either fezolinetant dose.

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