

Elinzanetant improves sleep disturbance in menopausal women partially independently of reductions in vasomotor symptoms: post hoc analysis from clinical trials

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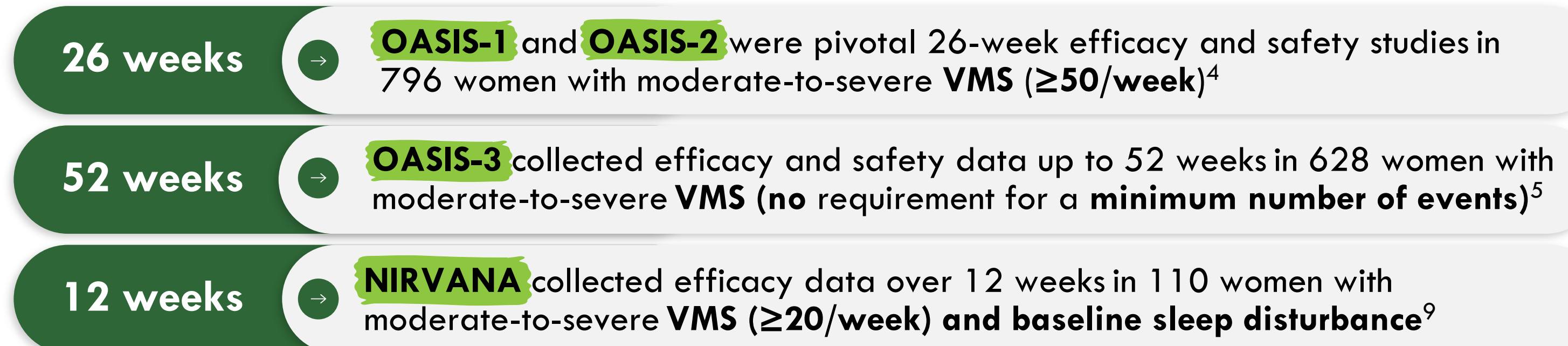
INTRODUCTION

- » Vasomotor symptoms (VMS) and sleep disturbance are among the most frequent **menopausal symptoms**.¹⁻³
- » VMS are **hot flashes** (or **night sweats** if they occur at night), **with or without sweating**. They are reported by **up to 80%** of women, with **up to 40%** reporting disruptive, moderate-to-severe symptoms.
- » Sleep disturbance (poor sleep quality, frequent awakenings, obstructive sleep apnea, restless legs syndrome, and insomnia) is reported by **up to 69%** of women.
- » Elinzanetant is a **selective dual neurokinin (NK)1 and NK3 receptor antagonist** that targets receptors found centrally in the **hypothalamus** and the **skin** to help bring balance back to temperature regulation and sleep.⁴⁻⁸
- » The **OASIS** and **NIRVANA** randomized, placebo-controlled trials investigated the effect of elinzanetant on VMS frequency/severity and sleep disturbance in menopausal women (**Figure 1**).^{4-6,9}
- » In OASIS-1 & -2, elinzanetant **significantly and rapidly reduced the frequency of moderate-to-severe VMS** from baseline to weeks 4 and 12 and from as early as week 1, and **significantly reduced Patient-Reported Outcomes Measurement Information System Sleep Disturbance Short Form 8b (PROMIS SD SF 8b) total score** from baseline to week 12 compared with placebo.⁴

METHODS

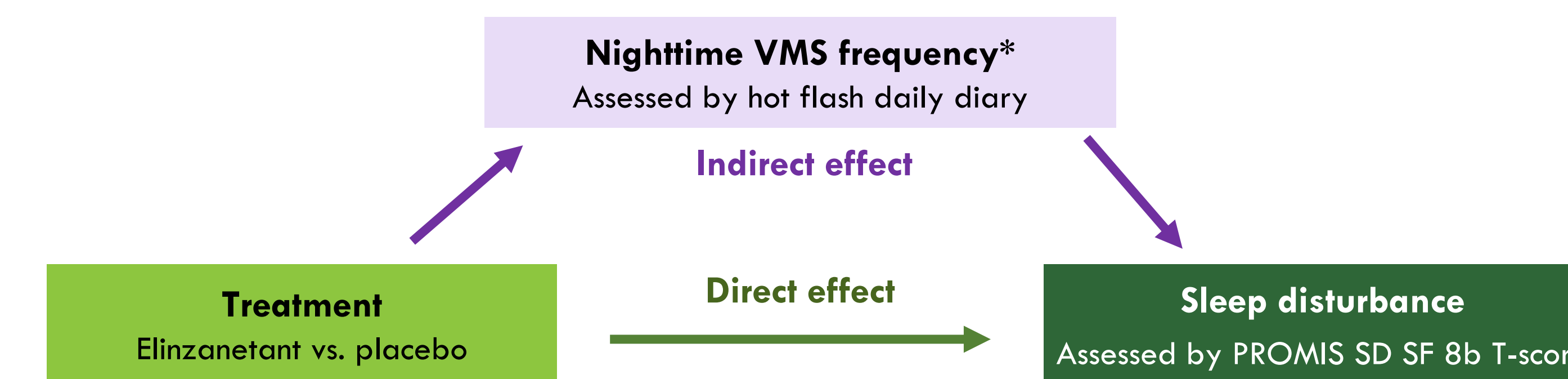
- » This post hoc causal mediation analysis included pooled data from OASIS-1, -2, and -3, and NIRVANA.^{4,5,9}
- » Linear mixed-effects models¹⁰ were applied to measurements at baseline and weeks 1, 2, 3, 4, 8, and 12.
- » A treatment-mediator interaction term was included to allow the effect of VMS on sleep disturbance to vary by treatment arm.
- » Analyses were controlled for plausible confounders, including baseline PROMIS SD SF 8b total score, baseline nighttime VMS frequency, age, body mass index, smoking history, and clinical trial.
- » Model coefficients were used to calculate:
 - » indirect effect of elinzanetant versus placebo on sleep disturbance via moderate-to-severe nighttime VMS frequency (**Figure 2**)
 - » direct effect of elinzanetant versus placebo on sleep disturbance independent of any effect on nighttime VMS frequency (**Figure 2**)
 - » total effect (elinzanetant versus placebo) on sleep disturbance.

Figure 1. Details of clinical trials included in the analysis



VMS, vasomotor symptoms.

Figure 2. Direct and VMS-mediated pathways between treatment and sleep disturbance



*Moderate-to-severe nighttime VMS frequency (weekly average). PROMIS SD SF 8b, Patient-Reported Outcomes Measurement Information System Sleep Disturbance Short Form 8b; VMS, vasomotor symptoms.

RESULTS

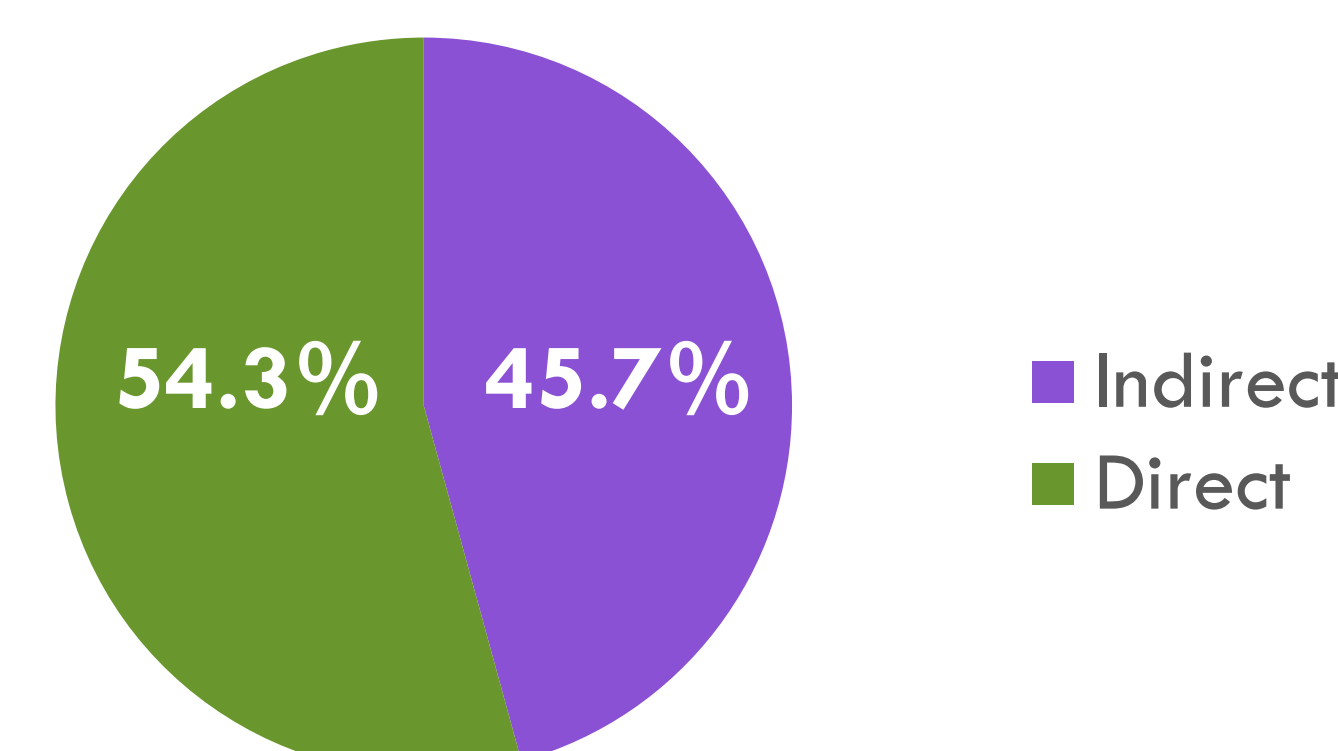
- » Data from **1,345** women were included in this analysis.
- » Improvements in sleep disturbance were **only partially explained** by reductions in moderate-to-severe nighttime VMS frequency, indicating **both direct and indirect** effects of elinzanetant.
- » The model results suggest that **approximately half** of the total treatment effect of elinzanetant on sleep disturbance is attributable to **direct effects (54.3%; Table 1 and Figure 3)**.

Table 1. Direct and indirect effects of elinzanetant on sleep disturbance

Effect	Mean difference vs. placebo (95% CIs)
N=1,345*	
Indirect (via VMS)	-2.25 (-2.81, -1.69)
Direct treatment effect on sleep	-2.67 (-3.28, -2.07)
Total	-4.92 (-5.73, -4.12)
% of total that is direct	54.3% (45.8%, 62.8%)

*Observed women with at least one visit within week 1, 2, 3, 4, 8, or 12 (and still on treatment). CI, confidence interval; VMS, vasomotor symptoms.

Figure 3. Proportion of total treatment effect on sleep disturbance: direct vs. indirect (VMS-mediated) effects



VMS, vasomotor symptoms.

CONCLUSIONS

This post hoc analysis (N=1,345) suggests that elinzanetant may have a **direct treatment effect on sleep disturbance (~54.3%) that is not solely related to reductions of nighttime VMS.**

These findings highlight the potential for elinzanetant to improve sleep through mechanisms beyond VMS reduction.

This supports the notion that sleep disturbance in menopause may not be solely caused by VMS.

Limitations of this analysis included reliance on self-reported sleep outcomes and possible lack of generalizability to women outside the age range/inclusion criteria, with more complex comorbidities.

Clinical implications: if sleep is improved through direct mechanisms, treatment choice for women with sleep complaints but less severe VMS may change.

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