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Effect of elinzanetant, an NK-1/NK-3 receptor antagonist, on patient-reported sleep disturbances: findings from two pivotal phase 3 studies

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INTRODUCTION

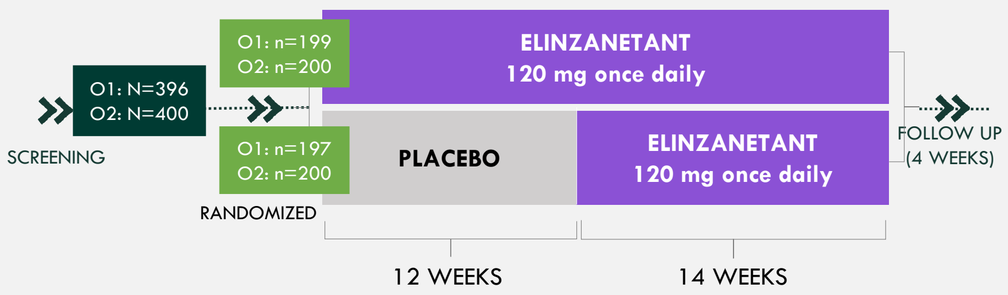
Elinzanetant (EZN), a non-hormonal dual neurokinin-1 and -3 receptor antagonist, is in development for the treatment of vasomotor symptoms (VMS) associated with menopause. This analysis aimed to describe the effect of EZN on sleep disturbances in women with moderate-to-severe VMS across two phase 3 trials (OASIS 1 and OASIS 2) and characterize its impact on sleep disturbances stratified by baseline levels of insomnia symptoms.

METHODS

Participants and interventions

Postmenopausal women experiencing ≥50 moderate-to-severe VMS per week were randomized 1:1 to receive EZN 120 mg or placebo (**Figure 1**). There was no pre-defined threshold for sleep disturbance severity to enter the studies.

Figure 1. OASIS 1 and 2 clinical study design



Main outcome measures (based on data from OASIS 1 and 2)

The Patient-Reported Outcomes Measurement Information System Sleep Disturbance Short Form 8b (PROMIS SD SF 8b) questionnaire and the Insomnia Severity Index (ISI) were used to assess the severity of sleep disturbance and insomnia, respectively (**Figures 2, 3, and 4**).

- PROMIS SD SF 8b items were scored on a 5-point Likert scale. Items were assessed individually or summed to yield total raw scores, which were then converted to total T-scores (range 28.9–76.5; higher scores indicated more severe sleep disturbances).
- The seven items of the ISI were scored on a 5-point Likert scale and summed to produce a total score (range 0–28; higher scores indicated more severe insomnia).

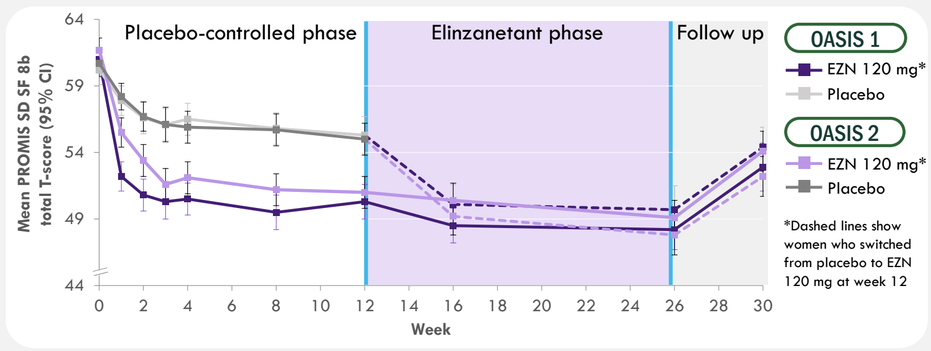
Both measures were completed electronically at baseline and weeks 4, 8, 12, 16, and 26 (the PROMIS SD SF 8b was additionally completed at weeks 1, 2, and 3).

Additional analyses (based on pooled data)

A secondary inferential analysis of pooled data from OASIS 1 and 2 with a mixed model for repeated measures was conducted to assess change in PROMIS SD SF 8b total T-scores and ISI total scores from baseline to week 12 for EZN vs. placebo. The presented one-sided p values were indicative but not confirmatory.

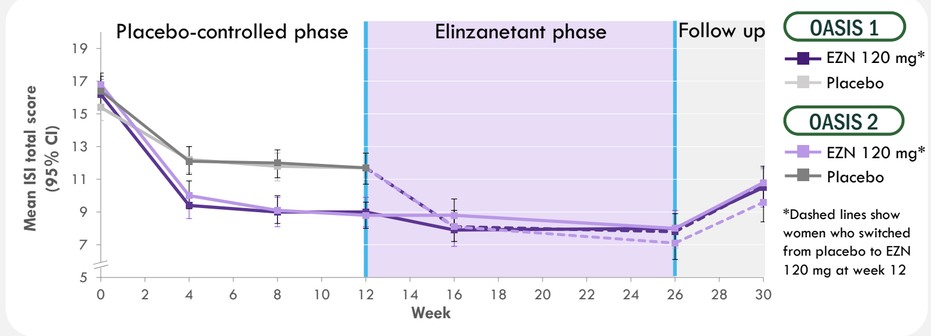
RESULTS

Figure 2. PROMIS SD SF 8b total T-scores over time



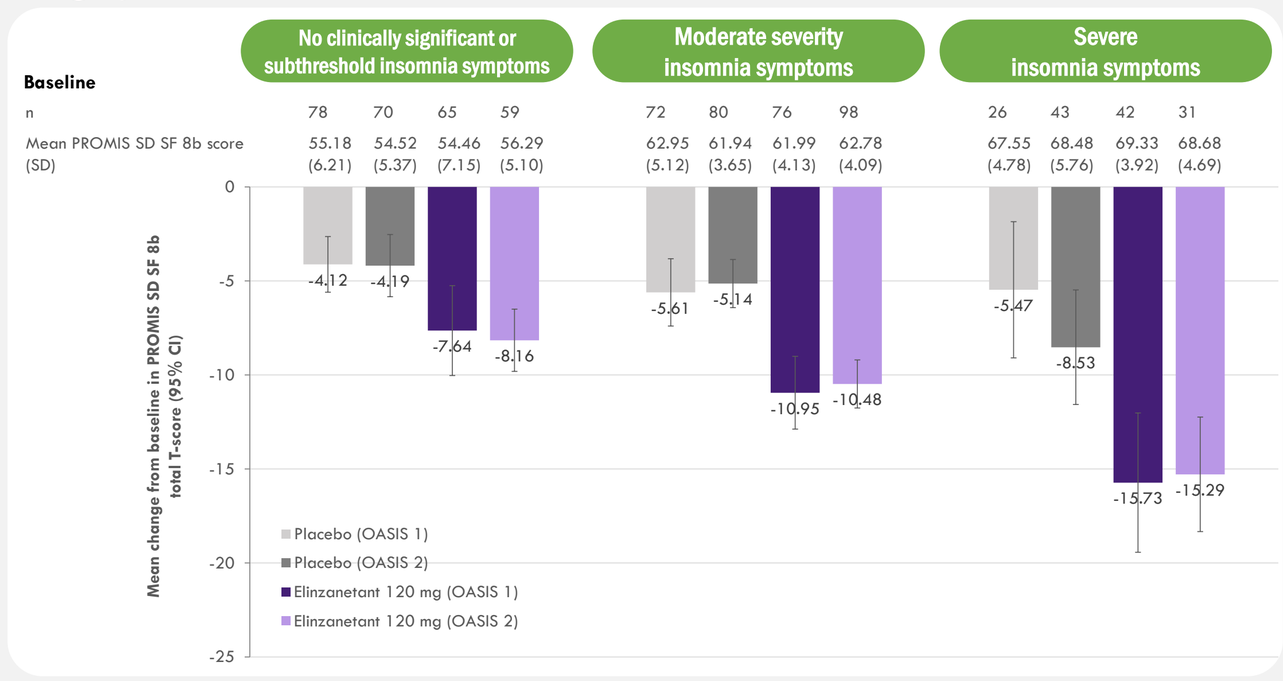
- Baseline mean (SD) PROMIS SD SF 8b T-scores in OASIS 1 and 2 were 61.0 (7.7)–61.7 (6.2) in the EZN group and 60.2 (7.2)–60.7 (7.2) for placebo; decreasing to 50.3 (8.8)–51.0 (7.9) and 55.3 (8.7)–55.0 (8.0), respectively, by week 12.

Figure 3. ISI total scores over time



- Baseline mean (SD) ISI total scores in OASIS 1 and 2 were 16.2 (6.1)–16.8 (5.1) in the EZN group and 15.4 (5.7)–16.4 (6.0) for placebo; decreasing to 9.0 (6.0)–8.8 (5.5) and 11.7 (6.1)–11.7 (6.3), respectively, by week 12.

Figure 4. Change from baseline in PROMIS SD SF 8b total T-score by baseline ISI category at week 12



ISI score categories: 0–17 no clinically significant or subthreshold insomnia symptoms; 15–21 moderate severity insomnia symptoms; 22–28 severe insomnia symptoms[1]

Additional analyses (based on pooled data):

- Changes from baseline in mean PROMIS SD SF 8b total T-score were nominally significant at week 12 for EZN vs. placebo (between group difference in least-squares means [95% CI]: -4.9 [-6.0, -3.9], p<0.0001).
- Changes from baseline in mean ISI total score were nominally significant at week 12 for EZN vs. placebo (between group difference in least-squares means [95% CI]: -2.9 [-3.7,-2.2], p<0.0001).

CONCLUSIONS

EZN reduced sleep disturbances and insomnia symptoms in a population not specifically selected for these sleep issues, supporting the benefit of EZN beyond VMS in postmenopausal women

Reductions were seen across both PROMIS SD SF 8b and ISI symptom measures, demonstrating a robust effect of EZN on sleep disturbances and insomnia symptoms

Reductions in sleep disturbances were observed across all insomnia symptom severity categories. Participants with the most severe insomnia symptoms noted the greatest reductions

Pooled analysis findings further demonstrate the effect of EZN on sleep disturbances and insomnia symptoms, which were found to be significant in key secondary and showed numerical improvements in exploratory endpoint analyses in OASIS 1 and 2[2]

ACKNOWLEDGEMENTS

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1. Morin C, et al. Sleep 2011;34:601–8
2. Pinkerton JV, et al. JAMA 2024. doi:10.1001/jama.2024.14618

DISCLOSURES

Pauline Maki has performed consultancy work for Abbott, Astellas, Bayer HealthCare AG, and Pfizer and received speaking honorarium from: Mithra. Equity in MidiHealth, Estrigenix, and re-spin. Hadine Joffe received grants from: NIH, Merck, Pfizer and has performed consultancy work for: Bayer, Merck, Hello Therapeutics. JoAnn V. Pinkerton was principal investigator on the OASIS 2 clinical trial, fees to the University of Virginia and has been a consultant with Bayer HealthCare Pharmaceuticals, and Pfizer. James A. Simon was principal investigator on the OASIS 1 trial; has grant/research support from: AbbVie, Inc., Bayer Healthcare LLC., Daré Bioscience, Ipsen, Mylan/Viatris Inc., Myovant Sciences, ObsEva SA, Sebela Pharmaceuticals Inc., Viveve Medical; has been a consultant/advisory boards of: Bayer HealthCare Pharmaceuticals Inc., Besins Healthcare, California Institute of Integral Studies (CIIS), Camargo Pharmaceutical Services, LLC, Covance Inc., Daré Bioscience, DEKA M.E.L.A S.r.l., Femasys Inc., KaNDy/NeRRe Therapeutics Ltd., Khyria, Madorra Pty Ltd., Mitsubishi Tanabe Pharma Development America, Inc., QUE Oncology Pty, Limited, Scynexis Inc., Sebela Pharmaceuticals, Inc., Sprout Pharmaceuticals, Inc., Vella Bioscience Inc.; has served on the Speaker's bureaus of: Mayne Pharma, Inc., Myovant Sciences, Inc., Pfizer Inc., Pharmavite LLC., Scynexis Inc., TherapeuticsMD; and is a stockholder (direct purchase) in: Sermonix Pharmaceuticals. Rebecca C. Thurston has an advisory role for: Astellas, Bayer, Hello Therapeutics. Cecilia Caetano and Lineke Zuurman are employees of Bayer CC, Basel, Switzerland. Susanne Parke, Christian Seitz, and Claudia Haberland are employees of Bayer AG, Berlin, Germany. Nazanin Haseli Mashhadi is an employee of Bayer PLC, Reading, UK. Ulrike Krahn is an employee of Bayer AG, Wuppertal, Germany.