COMPARATIVE EFFICACY OF ELINZANETANT VERSUS OTHER NON-HORMONAL THERAPIES FOR THE TREATMENT OF MODERATE TO SEVERE VASOMOTOR SYMPTOMS ASSOCIATED WITH MENOPAUSE – A NETWORK META-ANALYSIS

ELINZANETANT

Jenifer Sassarini[1, 2], Lee P. Shulman[3], Andromachi Giannopoulou[4], Piotr Wojciechowski[5], Klaudia Kolonko[5], Kristina Rosa Bolling[6], Vikram Talaulikar[7]

[1] NHS Greater Glasgow and Clyde, Glasgow, UK; [2] Department of Obstetrics and Gynaecology, School of Gynaecology, University of Glasgow, Glasgow, UK; [3] Feinberg School of Medicine of Northwestern University, Chicago, IL, USA; [4] Bayer Consumer Care AG, Basel, Switzerland, [5] Clever-Access, Krakow, Poland; [6] BAYER LLC, Tampa, Florida, US; [7] Institute of Women's Health, University College London, London, UK

INTRODUCTION & OBJECTIVE

- Vasomotor symptoms (VMS) affect up to 80% of women in the menopausal transition and last for a median of 7.4 years.[1]
- The long-term use of standard hormone therapies (HT) may be associated with an elevated risk of endometrial cancer and breast cancer, and thrombosis.[2-4]
- Non-hormonal pharmaceutical therapies (nHT) are alternatives for women who are not suitable candidates for HT or who do not wish to take HT.
- Approved nHTs include selective serotonin reuptake inhibitor (SSRI) paroxetine (PRX; US only), and neurokinin targeted therapy (NK-3 receptor antagonist) fezolinetant (FEZO).
- Other therapies, including serotonin-norepinephrine reuptake inhibitors (SNRI) and anticonvulsants, although not indicated for VMS are used to alleviate VMS.
- Elinzanetant (EZN) is the first and only dual NK targeted therapy blocking NK-1 and NK-3 receptors with demonstrated statistically significantly greater reduction in the frequency and severity of moderate to severe VMS, improvements in sleep disturbance and menopause-related quality of life, compared with placebo.[5]
- The objective of this network meta-analysis (NMA) is to indirectly compare the clinical efficacy of elinzanetant versus other nHTs which may inform HTA decision-making.

METHODS

- A systematic literature review was performed in Medline, Embase, and Cochrane up to August 2024 to identify phase 2/3/4 randomized controlled trials (RCT) which investigated pharmacological nHTs used to manage moderate-to-severe VMS in women with natural menopause. Studies enrolling patients with a history of breast cancer, receiving aromatase inhibitors or anti-estrogens, or failing to specify these patients were not included in this NMA.
- Trials were required to report at least one of the following outcomes: change from baseline in VMS frequency and severity, sleep disturbances, or the Menopause-Specific Quality of Life (MENQOL) score. Outcomes were consistently analyzed at 12 weeks of treatment.
- Identified RCTs formed a network of treatments with placebo as a common reference.
- Treatments were compared using a Bayesian network meta-analysis (NMA).
- The fixed- and random-effect models with uninformative priors were tested, with the former one preferred based on lower values of the Deviance Information Criterion (DIC).
- The **base case** analysis was run with phase 3 trials and a **sensitivity analysis** (SA) with all identified RCTs, including a phase 2 clinical trial SWITCH-1, was conducted.
- The results were presented as mean differences (MD) and odds ratios (OR) for continuous and dichotomous outcomes, respectively, together with 95% Bayesian credible intervals (95% CrI).
- The estimates for between-treatment comparisons were considered statistically significant (hereafter called 'significant') when the 95% CrI did not cross 0 for MD and 1 for OR.

RESULTS

Systematic Literature Review

- Seventeen RCTs were identified of which 16 reported the outcomes at 12 weeks:
  - 3 assessed elinzanetant (EZN) 120mg,
  - 3 assessed fezolinetant (FEZO) 45mg, and
  - 2 assessed paroxetine (PRX) 7.5mg,
  - 5 assessed desvenlafaxine (DVS) 50-200mg.
  - 3 assessed gabapentin (GABA) 1200-1800mg,
- All studies included in the analysis were phase 3 RCTs, with the exception of the SWITCH-1 trial for EZN, which is a phase 2 RCT.
- Mean baseline age was comparable across the studies, ranging from 52 to 56 years.
- The baseline daily hot flash frequency exceeded 8 in all studies, ranging from 8.5 to 15.4 events per day.

TABLE 1 Characteristics of identified RCTs

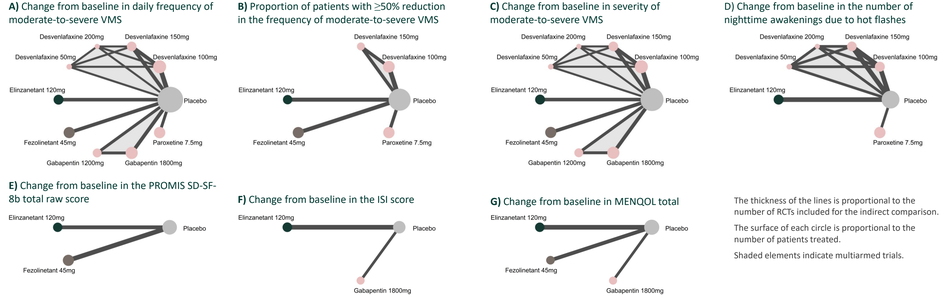
Study acronym or First author	Arms	Sample size	Treatment duration (weeks)	Mean age (years)	Mean number of hot flashes per day*
ELINZANETANT vs. Placebo					
SWITCH-1[6]	EZN 120mg	199	16	55.2	12.7
OASIS 1[5]	EZN 120mg	396	26	54.6	13.8
OASIS 2[5]	EZN 120mg	400	26	54.6	15.4
FEZOLINETANT vs. Placebo					
SKYLIGHT-1[10]	FEZO 45mg	348	52	54.5	10.5
SKYLIGHT-2[11]	FEZO 45mg	334	52	54.5	11.7
DAYLIGHT[12]	FEZO 45mg	453	27	54.5	10.7
SSRI vs. Placebo					
Pinkerton 2015a[7]	PRX 7.5mg	614	13	54.7	11.7
Pinkerton 2015b[7]	PRX 7.5mg	570	25	54.4	10.9
SNRI vs. Placebo					
Pinkerton 2013[13]	DVS 100mg	2,186	52	54.0	11.8
Archer 2009a[14]	DVS 100 & 150mg	458	14	53.4	10.8
Archer 2009b[15]	DVS 100 & 150mg	567	26	53.7	10.6
Bouchard 2012[16]	DVS 100mg	485	14	53.7	9.9
Speroff 2008[17]	DVS 50, 100, 150 & 200mg	707	54	53.5	10.9
GABAPENTIN vs. Placebo					
BREEZE 1[8]	GABA 1200 & 1800mg	541	12	52.9	13.2
BREEZE 2[8]	GABA 1200 & 1800mg	565	12	53.2	12.6
BREEZE 3[9]	GABA 1800mg	600	24	54.0	11.9

EZN – elinzanetant, DVS – desvenlafaxine, FEZO – fezolinetant, GABA – gabapentin, PRX – paroxetine, SSRI - selective serotonin reuptake inhibitor, * - mean baseline frequencies of hot flashes were calculated across all study groups.

OUTCOME REPORTING

- 15 RCTs (16 for SA, Fig. 1A) reported on VMS frequency, 12 (13 for SA, Fig. 1B) on VMS severity, 7 (8 for SA, Fig. 1D) on the number of nighttime awakenings due to hot flashes, 5 on sleep disturbances assessed using PROMIS-SD-SF-8b total raw core (Fig. 1E), 3 (4 for SA, Fig 1F) on insomnia severity index (ISI), and 6 (7 for SA, Fig. 1G) on MENQOL.

Figure 1 Evidence networks for respective outcomes

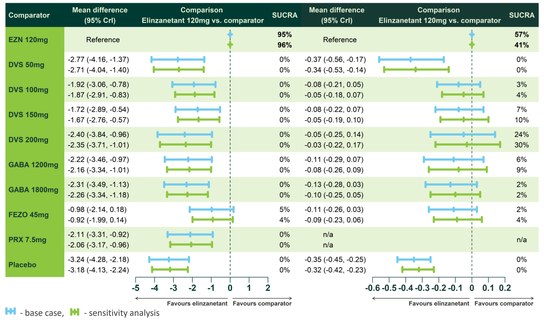


RESULTS OF THE NMA

EZN compared with other interventions showed:

- Change in daily VMS frequency (Fig. 2A)
  - **Significantly greater** reduction compared with PRX, DVS, and GABA.
  - Non-significant difference versus FEZO.
- Proportion of patients with ≥50% reduction in VMS frequency
  - **Significantly higher** compared with PRX (OR=2.20) and DVS 100mg (OR=1.52).
  - No significant differences versus DVS 150mg and FEZO.
- Change in VMS severity (Fig. 2B)
  - **Significantly greater** reduction versus DVS 50mg.
  - No significant differences versus other treatments.
- Sleep disturbances
  - **Significantly greater** reduction in the mean number of nighttime awakenings compared with PRX (MD=-0.82) and all DVS regimens.
  - **Significant improvement** in PROMIS SD 8b total raw score versus FEZO (MD=-2.67).
  - No significant difference in reducing ISI versus GABA 1800mg.
- Quality of life
  - No significant difference in MENQOL changes across treatments.

Figure 2 Forest plots for comparison between EZN and comparators on VMS frequency and severity



- base case, - sensitivity analysis

EZN – elinzanetant, DVS – desvenlafaxine, FEZO – fezolinetant, GABA – gabapentin, PRX – paroxetine, SUCRA - surface under the cumulative ranking curve

CONCLUSIONS

- Elinzanetant has the highest probability of being the most effective treatment for reducing the frequency and severity of VMS (SUCRA) and
- Elinzanetant statistically significant improvement in sleep disturbance (PROMIS-SD-SF 8b).

Therefore, EZN is a promising option for women seeking relief from menopausal symptoms. The results should be interpreted in the context of estimates being derived from an indirect comparison.

BIBLIOGRAPHY

1. doi: 10.1016/j.ogc.2018.07.0052.
2. doi: 10.1001/jama.288.3.321
3. doi: 10.1002/14651858.CD004143.pub5
4. doi: 10.1001/jama.2013.2780405.
5. doi:10.1001/jama.2024.14618
6. doi: 10.1097/gme.0000000000002138
7. doi: https://dx.doi.org/10.1097/GME.0000000000000311
8. https://beta.clinicaltrials.gov/study/NCT00755417202 3
9. doi: https://dx.doi.org/10.1097/GME.0b013e3182a7c073
10. doi: 10.1016/s0140-6736(23)00085-5
11. doi: 10.1210/clinem/dgad058
12. doi: 10.1136/bmj-2024-079525
13. doi: https://dx.doi.org/10.1097/gme.0b013e31826421a8
14. doi: https://dx.doi.org/10.1016/j.ajog.2008.09.877
15. doi: https://dx.doi.org/10.1016/j.ajog.2008.10.057
16. doi: https://dx.doi.org/10.3109/13697137.2011.586445
17. doi: https://dx.doi.org/10.1097/01.AOG.0000297371.89129.b3

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