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ELINZANETANT FOR HOT FLASHES DURING THERAPY IN HR-POSITIVE BREAST CANCER

Schweizerische Gesellschaft für Gynäkologische Endokrinologie, Kontrazeption und Menopause

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Cardoso F, Parke S, Brennan DJ, Briggs P, Donders G, Panay N, Haseli-Mashhadi N, Block M, Caetano C, Francuski M, Haberland C, Laapas K, Seitz C, Zuurman L.

Elinzanetant for Vasomotor Symptoms from Endocrine Therapy for Breast Cancer.

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BACKGROUND

Endocrine therapies, such as tamoxifen and aromatase inhibitors, are essential in the adjuvant treatment of hormone receptor-positive (HR+) breast cancer. While they significantly reduce recurrence and mortality rates, they also have significant side effects, particularly vasomotor symptoms (VMS), which affect 60–80% of patients. These symptoms negatively impact quality of life and adherence, which can then worsen the prognosis. As hormone therapy is not suitable for symptom relief, there is a clinical need for effective non-hormonal alternatives. The non-hormonal pharmacotherapies currently recommended for VMS (antidepressants, anticonvulsants and anticholinergics) are used off-label (1).

Elinzanetant is an oral neurokinin-1 and -3 receptor antagonist that modulates KNDy neurons in the hypothalamus to influence thermoregulation. Earlier phase 3 studies (OASIS-1 to -3) have already demonstrated a significant reduction in menopausal symptoms in postmenopausal women. This raises the question of the extent to which elinzanetant reduces the frequency and severity of VMS and associated sleep disturbances in women receiving endocrine therapy for HR+ breast cancer, compared with a placebo.

TRIAL

The multicentre, randomised, double-blind, placebo-controlled Phase 3 study (OASIS-4; NCT05587296) included 474 women aged 18–70 years. The inclusion criteria were the receipt of ≥5 years of endocrine therapy for HR+ breast cancer or its prevention, and the experience of ≥35 moderate to severe VMS per week. Participants were randomised at a ratio of 2:1 to receive either elinzanetant (120 mg daily) or placebo for 12 weeks, followed by elinzanetant for 40 weeks.

- Primary endpoints: Change in the mean daily frequency of moderate to severe VMS from baseline to weeks 4 and 12.
- Secondary endpoints: PROMIS SD SF 8b (sleep disturbances; scale 28.9–76.5), MENQOL (quality of life; scale 1-8).

A total of 474 women were enrolled in the study and randomised in a 2:1 ratio. Of these, 316 received elinzanetant 120 mg daily for 52 weeks, while 158 initially received placebo for 12 weeks, followed by elinzanetant for an additional 40 weeks.

At the start of the study, the average daily frequency of moderate to severe VMS was 11.4 episodes in the elinzanetant group and 11.5 episodes in the placebo group. After just four weeks, a significant reduction in VMS was observed with elinzanetant, averaging 6.5 episodes per day (95% CI: −7.2 to −5.8), whereas the reduction in VMS under placebo was only 3.0 episodes per day (95% CI: −3.9 to −2.2). The difference between the two groups was 3.5 episodes per day (95% CI: −4.4 to −2.6; $p < 0.001$). After 12 weeks, the number of daily VMS episodes had decreased by an average of 7.8 (95% CI: –8.5 to –7.1) in the elinzanetant group compared to a decrease of 4.2 (95% CI: –5.2 to –3.2) in the placebo group. The resulting difference was 3.4 episodes per day (95% CI: −4.2 to −2.5; $p < 0.001$).

Elinzanetant also showed benefits in terms of secondary endpoints. The PROMIS SD SF 8b score, which measures the severity of sleep disturbances, improved by an average of 10.6 points (95% CI: −11.5 to −9.6), whereas the improvement observed with placebo was only 4.1 points (95% CI: −5.3 to −2.9). The difference between the groups was −6.1 points (95% CI: −7.5 to −4.8; $p < 0.001$).

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In terms of menopause-specific quality of life, as measured by the MENQOL questionnaire, there was an improvement of 1.3 points (95% CI: –1.4 to –1.2) compared to an improvement of 0.5 points (95% CI: –0.7 to –0.3) in the placebo group. The difference was 0.7 points (95% CI: −0.9 to −0.5; $p < 0.001$).

A relevant clinical response, defined as a ≥50% reduction in vasomotor symptom (VMS) frequency, was observed in week 4 in 61.1% of women in the elinzanetant group (95% CI: 55.7–66.6%), compared to 27.0% in the placebo group. By week 12, this proportion had increased to 74.3% (95% CI: 69.3–79.3) in the elinzanetant group versus 35.8% (95% CI: 29.2–42.4) in the placebo group.

In terms of safety, adverse events occurred in 69.8% of participants receiving elinzanetant during the first 12 weeks, compared to 62.0% of those receiving placebo. Most events were mild to moderate in severity. Serious adverse events were reported by 4.1% of those receiving elinzanetant versus 2.5% of those receiving placebo, while they occurred in 2.5% of the former group and 0.6% of the latter. The most common side effects associated with elinzanetant were somnolence (10.8%), fatigue (9.5%) and headache (9.5).

With regard to endometrial safety, all 33 women with abnormal findings who underwent an endometrial biopsy while taking elinzanetant had benign histological results.

Similarly, there were no indications of clinically relevant hepatotoxic effects. Elinzanetant also had no effect on the pharmacokinetics of tamoxifen and aromatase inhibitors. The reverse is also true: tamoxifen and aromatase inhibitors had no effect on the pharmacokinetics of elinzanetant.

COMMEND

This study demonstrates, with high statistical significance, that elinzanetant rapidly (within one week) and sustainably reduces the frequency and severity of vasomotor symptoms (VMS) over 12 weeks. This effect was also observed in relevant secondary endpoints, such as sleep disturbances and quality of life - both of which are significant factors in adherence to endocrine therapy. Tolerability was good, with a side-effect profile comparable to placebo. Hepatic events were rare and reversible. Therefore, elinzanetant is an effective and safe non-hormonal treatment option for VMS in women receiving endocrine therapy for HR-positive breast cancer. Approval and market launch are expected in 2025.

REFERENCES

(1) „The 2023 Nonhormone Therapy Position Statement of The North American Menopause Society" Advisory Panel.
The 2023 nonhormone therapy position statement of The North American Menopause Society.
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