Efficacy and safety of elinzanetant for vasomotor symptoms associated with endocrine therapy: Phase III OASIS-4 trial

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Disclosures

Fatima Cardoso declares paid consultancy for: Amgen, Astellas/Medivation, AstraZeneca, Bayer, Celgene, Daiichi-Sankyo, Eisai, GE Oncology, Genentech, Gilead, GlaxoSmithKline, Iqvia, Macrogenics, Medscape, Merck-Sharp, Merus BV, Mylan, Mundipharma, Novartis, Pfizer, Pierre-Fabre, prIME Oncology, Roche, Sanofi, Samsung Bioepis, Seagen, Teva, Touchime.

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Key takeaway points

Elinzanetant **significantly reduced VMS (hot flash) frequency** and **numerically reduced VMS severity** vs placebo in women receiving ET for HR+ breast cancer

Improvements were seen early, and treatment effects were **maintained up to 52 weeks**

Elinzanetant was **well tolerated** for the duration of the study

Similar safety profile to women without breast cancer and with VMS due to natural or surgical induced menopause

Effective VMS management may support **better quality of life** and potentially support patient's adherence to their endocrine therapy

ET, endocrine therapy; HR+, hormone receptor-positive; VMS, vasomotor symptoms.

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Background

- VMS (hot flashes) are common in women receiving ET for HR+ breast cancer and can be more severe than those associated with natural menopause.[1] **VMS and sleep disturbances** often co-occur and are associated with **reduced quality of life and cognitive function**[2]
- These symptoms are a **key contributor to non-adherence to ET**, with discontinuation usually around 30%, with some reports as high as 60%[1,3]
- **Menopausal hormone therapy is contraindicated** in this population due to the risk of breast cancer recurrence[4]
- **No therapies are currently approved** specifically for VMS in women with HR+ breast cancer, underscoring an unmet need.[1] Antidepressants and acupuncture are sometimes used[4]
- **Elinzanetant**, a **dual neurokinin-targeted therapy** (NK-1 and NK-3 receptor antagonist), **improved VMS, sleep disturbances, and menopause-related quality of life** in women undergoing **natural menopause** in the OASIS-1 -2, and -3 Phase III trials[5,6]

ET, endocrine therapy; HR+, hormone receptor-positive; NK, neurokinin; VMS, vasomotor symptoms.

1. Kingsberg S, *et al. Maturitas* 2024;188:108071; **2.** Van Dyk K, *et al. Curr Opin Endocr Metab Res* 2021;18:165–70; **3.** Smith KL, *et al. npj Breast Cancer* 2022;8:53; **4.** Biglia N, *et al. Ecancermedicalscience* 2019;13:909; **5.** Pinkerton JV, *et al. JAMA* 2024;332(16):1343–54; 6. Panay N, et al. Menopause 2024;31(12):1100-69.

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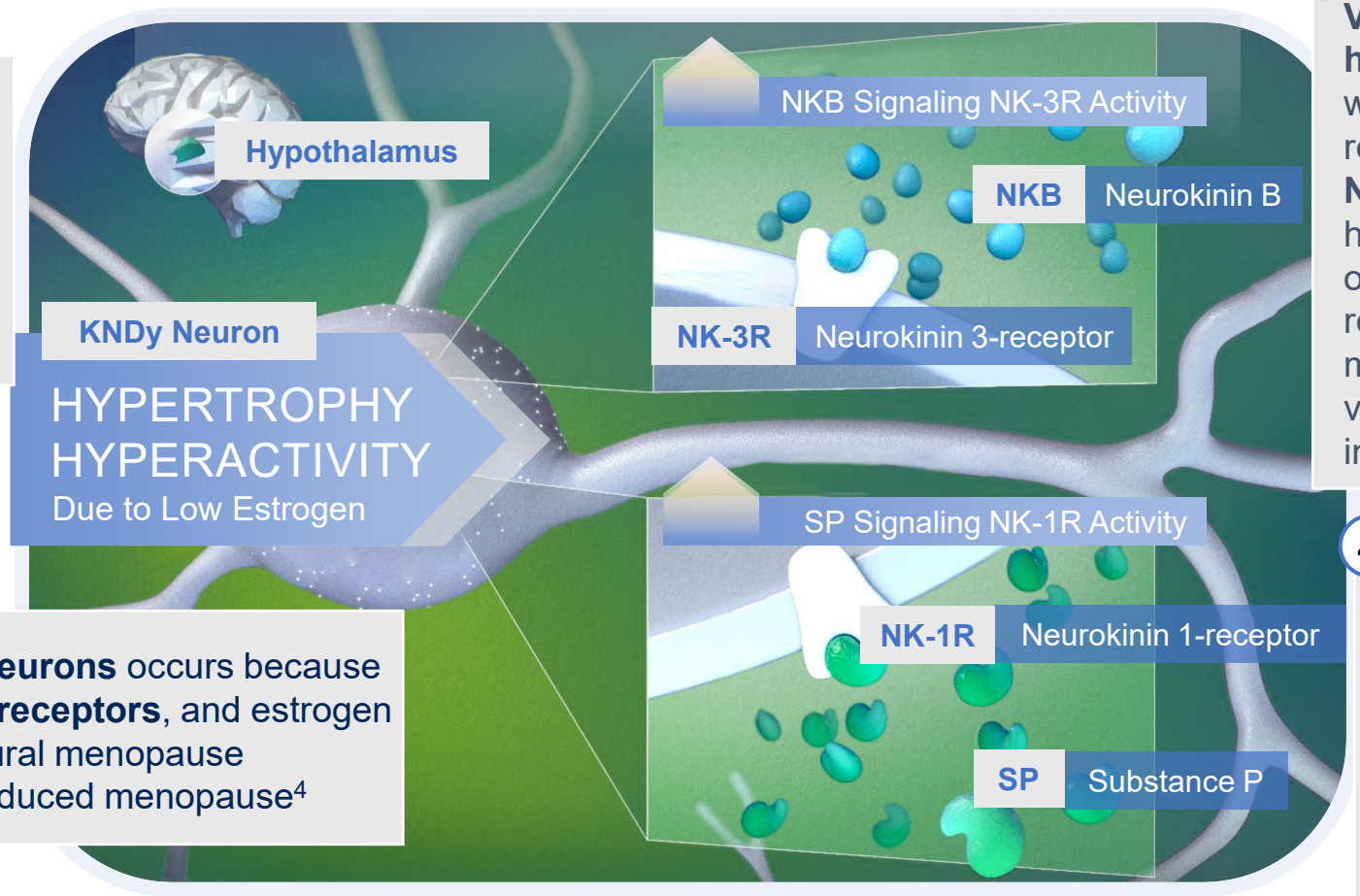
Theorized science of VMS

1 Specific neurons called **KNDy neurons**, located in the **hypothalamus**, are thought to play a **key role in thermoregulation and sleep**[1-3]



2 **VMS are thought to be caused by hyperactivity of KNDy neurons**, in which several neuropeptides and receptors are upregulated, including **NK-1 and NK-3 receptors**. This hyperactivity leads to dysregulation of the thermoregulatory center resulting in VMS.[4-11] NK-1 receptors may have a role in peripheral vasodilatation and primary insomnia.[12]

3 Hyperactivity of **KNDy neurons** occurs because they **express estrogen receptors**, and estrogen levels decline in the natural menopause transition or as part of induced menopause[4]

4 Targeted **dual antagonism of NK-1 and NK-3 receptors decreases the frequency and severity of VMS** and **sleep disturbances**[12]

KNDy, kisspeptin neurokinin B dynorphin; VMS, vasomotor symptoms

1. Modi M et al. Semin Reprod Med 2019;37:125–30; 2. Navarro VM et al. Endocrinology 2015;156:627–37; 3. Padilla SL et al. Curr Biol 2019;29:592–604.e1–e4; 4.Rance NE, et al. Front Neuroendocrinol 2013;34(3):211-227; 5. Sergeeva OA, et al. Peptides 2022;150:170729; 6. Modi M, et al. Semin Reprod Med 2019;37:125-30; 7. Rance NE, et al. Endocrinol 1991;128:2239-47; 8. Wong BJ, et al. J Physiol 2006;577:1043-51; 9. Mittleman-Smith MA, et al. Proc Natl Acad Sci USA 2012;109:19846-54; 10. Sassarini J, et al. Exp Opin Invsetig Drugs 2024;33:19-26; 11. Crandall CJ, et al. Menopause 2017;24:252-61; 12. Pinkerton JV, et al. JAMA 2024;332(16):1343–54

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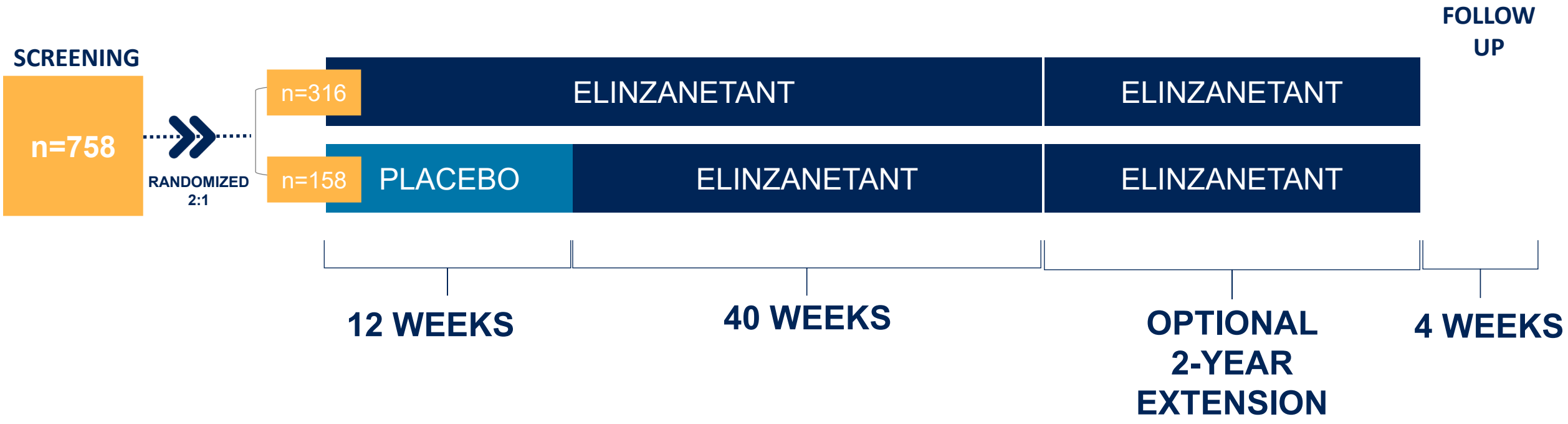
Methods – Trial design

OASIS-4 (NCT05587296) is a **multicenter, randomized, double-blind, placebo-controlled** Phase III trial evaluating elinzanetant 120 mg for the treatment of **VMS associated with ET in women with or at high risk of HR+ breast cancer**[1,2]



ET, endocrine therapy; HR+, hormone receptor-positive; VMS, vasomotor symptoms.

1. Cardoso F, *et al*. Poster presented at ESMO Breast Cancer Congress; May 11–13, 2023; Berlin, Germany; **2.** ClinicalTrials.gov. NCT05587296. Available from: https://clinicaltrials.gov/study/NCT05587296. Accessed April 8, 2025.

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Methods – Eligibility criteria[1,2]

Key inclusion criteria

- Women aged 18–70 years
- Women experiencing **VMS due to ET** that they are expected to use for the duration of the study:
  - Tamoxifen with or without the use of GnRH analogs, or
  - Aromatase inhibitors with or without the use of GnRH analogs
- Women must have a **personal history of HR+ breast cancer or be at high risk for developing breast cancer**
- Women must complete the **hot flash daily diary** for at least 11 days during the two weeks before the baseline visit and **report ≥35 moderate-to-severe hot flashes per week, including nighttime episodes**

Definitions of VMS:

Mild: sensation of heat without sweating
Moderate: sensation of heat with sweating
Severe: sensation of heat with sweating and causing cessation of activity

ET, endocrine therapy; GnRH, gonadotropin-releasing hormone; HR+, hormone receptor-positive; VMS, vasomotor symptoms.

1. Cardoso F, *et al*. Poster presented at ESMO Breast Cancer Congress; May 11–13, 2023; Berlin, Germany; **2.** ClinicalTrials.gov. NCT05587296. Available from: https://clinicaltrials.gov/study/NCT05587296. Accessed April 8, 2025.

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Methods – Outcomes[1,2]

Primary Endpoints	Key Secondary Endpoints	Secondary Endpoints	Safety
• **Mean change in average daily frequency of moderate-to-severe VMS from baseline to weeks 4 and 12** • These were analyzed using a mixed model with repeated measures (two-sided p-values)	• **Mean change in PROMIS SD SF 8b total T-score from baseline to week 12** • **Mean change in MENQOL total score from baseline to week 12** • These were analyzed using a mixed model with repeated measures (two-sided p-values) and included in the hierarchical testing strategy	• **Mean change** in average **daily frequency of moderate-to-severe VMS** from **baseline to week 1 and over time** • **Mean change** in average **daily severity of moderate-to-severe VMS** from **baseline to weeks 4 and 12**	• **Treatment-emergent adverse events** were reported by participants throughout the study and analyzed descriptively

MENQOL, Menopause-Specific Quality of Life questionnaire; PROMIS SD SF 8b, Patient-Reported Outcomes Measurement Information System Sleep Disturbance Short Form 8b; VMS, vasomotor symptoms.

1. Cardoso F, *et al*. Poster presented at ESMO Breast Cancer Congress; May 11–13, 2023; Berlin, Germany; **2.** ClinicalTrials.gov. NCT05587296. Available from: https://clinicaltrials.gov/study/NCT05587296. Accessed April 8, 2025.

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Demographics and clinical characteristics

The majority of participants were white
- White: 88.0% (elinzanetant), 88.6% (placebo)
- Black/African American: 1.9% (elinzanetant), 0.6% (placebo)
- Hispanic/Latino: 2.2% (elinzanetant), 3.2% (placebo)

Mean (SD) age was balanced across groups
- 50.8 (7.5) in elinzanetant
- 51.5 (6.7) in placebo

Mean (SD) BMI was balanced across groups
- 26.1 (4.6) kg/m^2 in elinzanetant
- 26.8 (4.7) kg/m^2 in placebo

Most women were taking ET for breast cancer treatment
- 99.7% in elinzanetant
- 100% in placebo

	Elinzanetant (n=316)	Placebo (n=158)
Histology, n (%)		
Infiltrating duct carcinoma, NOS	219 **(69.3%)**	97 **(61.4%)**
Lobular carcinoma, NOS	37 **(11.7%)**	25 **(15.8%)**
Ductal carcinoma in situ, solid type	19 **(6.0%)**	9 **(5.7%)**
Other	41 **(13.0%)**	27 **(17.1%)**
Type of endocrine treatment, n (%)		
Tamoxifen	175 **(55.4%)**	90 **(57.0%)**
Aromatase inhibitors	141 **(44.6%)**	68 **(43.0%)**
Duration of endocrine therapy prior to study entry (months), median (min, max)	20.4 **(0.0, 97.2)**	18.0 **(1.2, 116.4)**

ET, endocrine therapy; NOS, not otherwise specified; SD, standard deviation.

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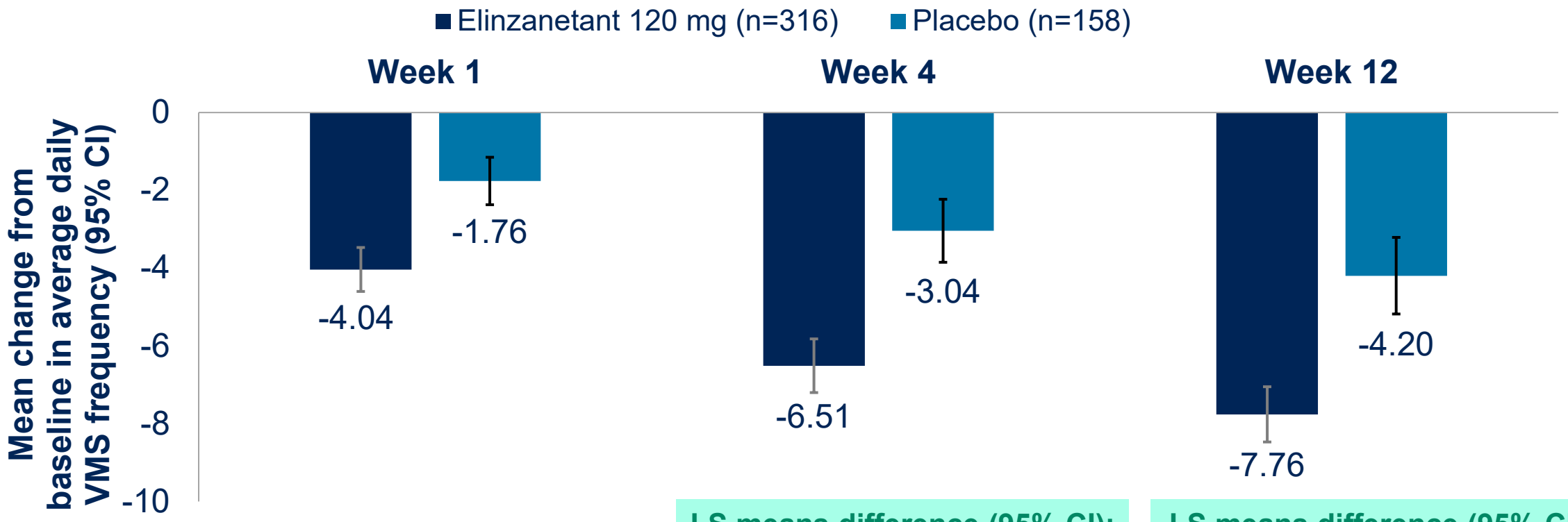
Results – Mean change from baseline in average daily moderate-to-severe VMS frequency

Mean (95% CI) baseline daily VMS frequency	Elinzanetant: 11.4 (10.7,12.2)	Placebo: 11.5 (10.5,12.5)



LS means difference (95% CI): -3.5 (-4.4, -2.6); p<0.0001

LS means difference (95% CI): -3.4 (-4.2, -2.5); p<0.0001

Note: 95% CI not adjusted for multiplicity
CI, confidence interval; LS, least squares; VMS, vasomotor symptoms.

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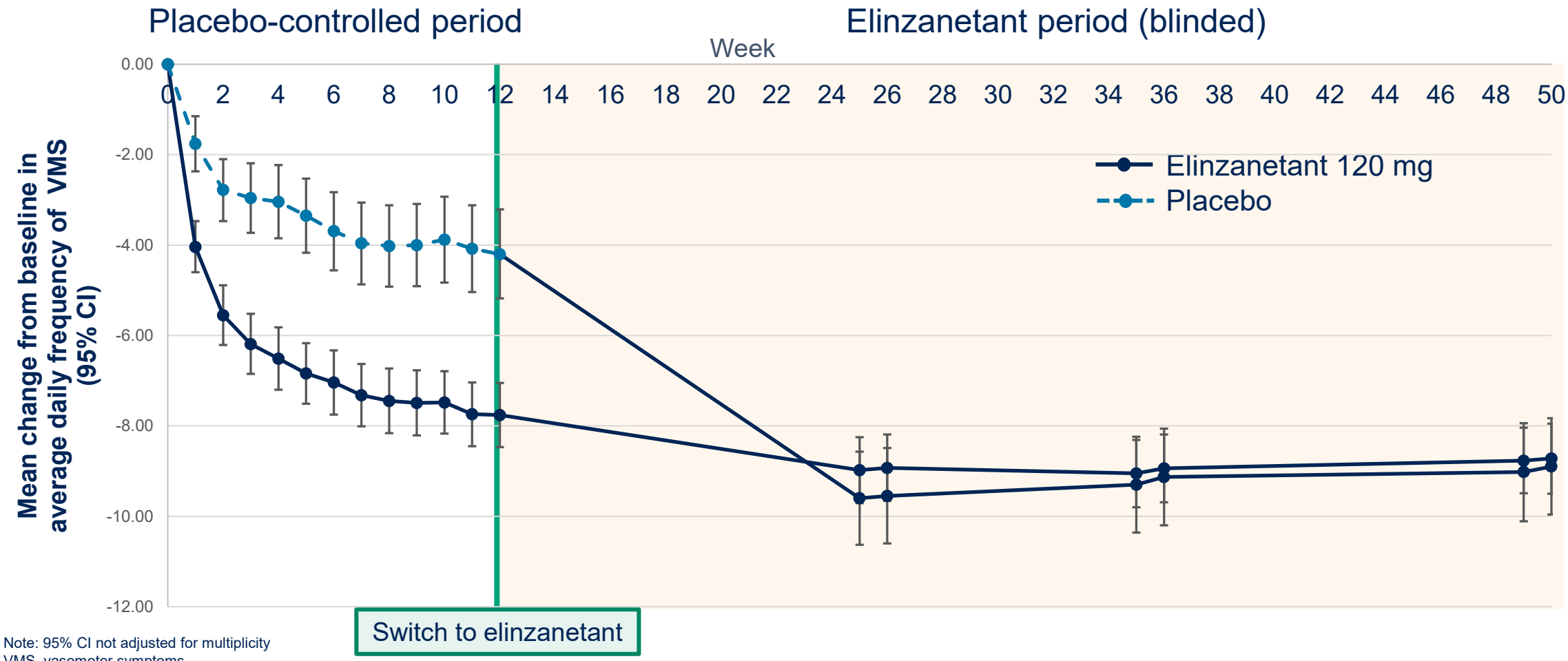
Results – Mean change from baseline in average daily moderate-to-severe VMS frequency over time



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VMS, vasomotor symptoms.

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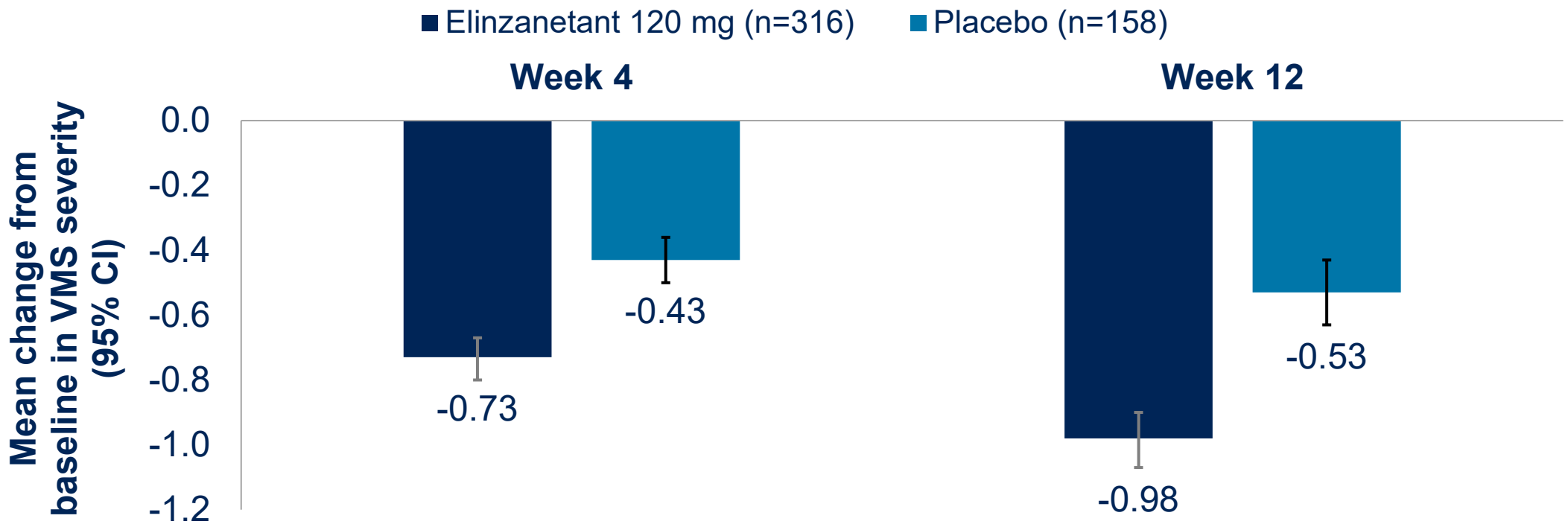
Results – Mean change from baseline in average daily moderate-to-severe VMS severity

Mean (95% CI) baseline daily VMS severity	Elinzanetant: 2.49 (2.5,2.5)	Placebo: 2.49 (2.5,2.5)



Note: 95% CI not adjusted for multiplicity
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Results – Safety

n (%)	Elinzanetant 120 mg Weeks 1–12 (n=315)	Placebo Weeks 1–12 (n=158)	Elinzanetant 120 mg Weeks 1–52 (N=465)
Any TEAE	220 **(69.8%)**	98 **(62.0%)**	368 **(79.1%)**
Headache	30 **(9.5%)**	20 **(12.7%)**	56 **(12.0%)**
Arthralgia	20 **(6.3%)**	10 **(6.3%)**	52 **(11.2%)**
Fatigue	30 **(9.5%)**	8 **(5.1%)**	43 **(9.2%)**
Somnolence	34 **(10.8%)**	6 **(3.8%)**	42 **(9.0%)**
Diarrhea	16 **(5.1%)**	3 **(1.9%)**	32 **(6.9%)**
Back pain	10 **(3.2%)**	7 **(4.4%)**	29 **(6.2%)**
Nausea	19 **(6.0%)**	10 **(6.3%)**	29 **(6.2%)**
Any serious TEAE	8 **(2.5%)**	1 **(0.6%)**	33 **(7.1%)**

TEAE, treatment-emergent adverse event.

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Limitations

Patient demographics

Most participants in the study were white; although this was consistent with the European population where most study sites were located, it limits the generalizability of findings to other populations

Insufficient data in patients at risk of developing breast cancer

Since **only one participant was taking ET for breast cancer prevention**, conclusions regarding the efficacy of elinzanetant in this population cannot be drawn

No assessment of breast cancer outcomes

Breast cancer recurrence and survival were not predefined outcomes in this study; future studies assessing these outcomes will be important

Exclusion of certain breast cancer subgroups

Patients with metastatic disease or recent surgical/medical treatment (<3 months) prior to informed consent were excluded and will need to be evaluated in further studies

ET, endocrine therapy; VMS, vasomotor symptoms.

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Conclusions

Elinzanetant is the first neurokinin-targeted therapy to demonstrate efficacy in reducing VMS in women receiving ET for HR+ breast cancer

Elinzanetant **significantly reduced VMS frequency and also numerically reduced VMS severity** vs placebo in women receiving ET for HR+ breast cancer

Elinzanetant demonstrated rapid and sustained effect

Symptom relief was observed **as early as week 1** and sustained through week 12; similar effects were observed in women switching from placebo to elinzanetant and **maintained throughout the study duration**

Elinzanetant was well tolerated

Favorable safety profile over 52 weeks, supporting its potential long-term use in this population.
Additional safety data are being collected in an **ongoing 2-year extension**
Further research on its eventual **impact on long-term breast cancer outcomes is important**

ET, endocrine therapy; HR+, hormone receptor-positive; VMS, vasomotor symptoms.

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Further results from the OASIS 4 clinical trial are being presented as a poster:

Abstract ID: 12063

Title: **Impact of elinzanetant on sleep disturbances and quality of life** in women undergoing adjuvant endocrine therapy for breast cancer: Phase 3 OASIS 4 trial

Time/date: 02 June at 1:30 PM-4:30 PM CT

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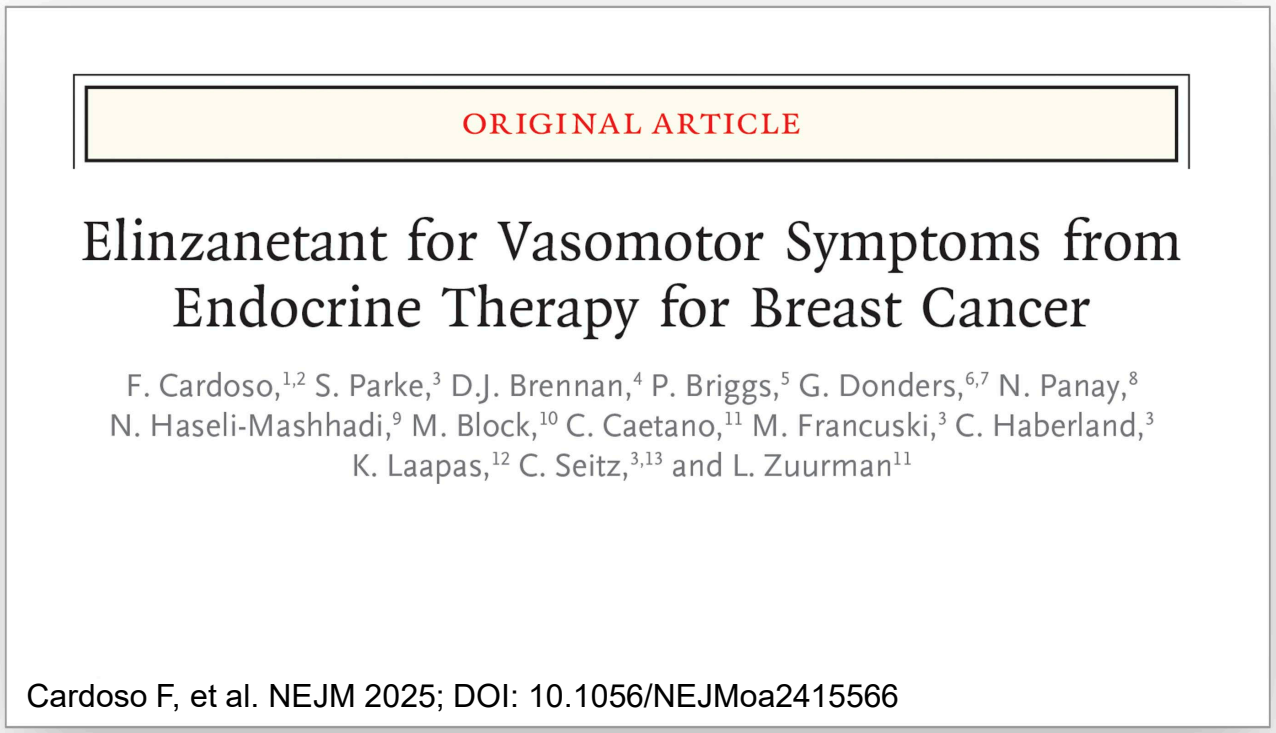
ORIGINAL ARTICLE

Elinzanetant for Vasomotor Symptoms from Endocrine Therapy for Breast Cancer

F. Cardoso,[1,2] S. Parke,[3] D.J. Brennan,[4] P. Briggs,[5] G. Donders,[6,7] N. Panay,[8] N. Haseli-Mashhadi,[9] M. Block,[10] C. Caetano,[11] M. Francuski,[3] C. Haberland,[3] K. Laapas,[12] C. Seitz,[3,13] and L. Zuurman[11]

Cardoso F, et al. NEJM 2025; DOI: 10.1056/NEJMoa2415566

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What this study means for patients

What did this research tell us?

This study showed that **elinzanetant**, a neurokinin-targeted therapy, helped **reduce the frequency and severity of hot flashes** in patients taking endocrine therapy for breast cancer. These improvements were seen early and lasted beyond 12 weeks, with treatment effects being maintained up to 52 weeks

Who does this research impact?

Patients who are receiving treatment for hormone receptor-positive (HR+) breast cancer and experiencing disruptive hot flashes due to their therapy. There is a significant unmet need for hormone-free treatment options in this population, and this was **the first study to investigate a neurokinin-targeted therapy to address that gap**

What does this mean for patients right now?

Menopause symptoms caused by breast cancer treatment can **impact quality of life**. **Elinzanetant** may offer **a non-hormonal option** to manage these symptoms **and improve quality of life** during treatment, potentially also supporting patients' **adherence** to their breast cancer treatment.

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The authors would like to thank all patients who participated in the OASIS 4 clinical trial as well as all centres, investigators and study teams

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