Targeting Neurokinin Pathways in Menopause VMS: Dual NK-1 and NK-3 Receptor Antagonism

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MA-M_ELZ-ALL-0161-1

EMJ European Medical Journal

VMS and Menopause

Up to **80% of women** experience **VMS symptoms,** with up to 40% of women reporting moderate-to-severe symptoms.[1-3]

80%♀

Nearly **two-thirds of women** have untreated moderate-to-severe **hot flashes**.[1]

2/3

Nearly **70%** struggle with **disrupted sleep** during menopause.[1,4-6]

70%

VMS can **significantly impact daily life**, linked to sleep and mood disturbance, impaired cognitive function, fatigue, anxiety, and depression.[1,3]

2/3

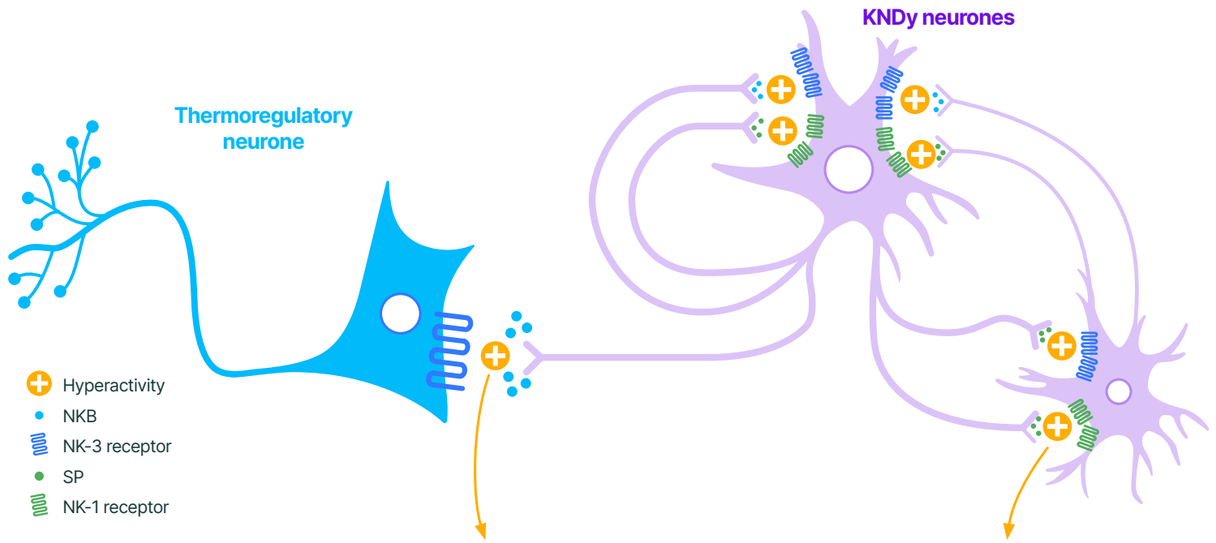
of women

worldwide go untreated due to fears, safety concerns, and not wanting available treatment options.[1,7]

Disruptive Menopause Symptoms Begin with Overactive NK-1 and NK-3 Pathways

Step 1: Trigger	Step 2: Response	Step 3: Outcome
During menopause, hyperactivity of KNDy neurones begins with upregulation of NK-1 and NK-3 receptors and their respective ligands, SP and NKB.[8,9]	NK-3: NKB binds to NK-3 receptors leading to dysregulation of the thermoregulatory centre of the hypothalamus, resulting in hot flashes. NK-1: SP binds to NK-1 receptors and is involved in sleep disturbances. Peripheral NK-1 receptors: Peripheral NK-1 receptors are also found on nerves associated with blood vessels in the skin and contribute to sweating and vasodilation as a cooling response to the increase in body temperature.[8-10]	VMS: Hot flashes during day and night and sleep disturbances.[9,11,12]

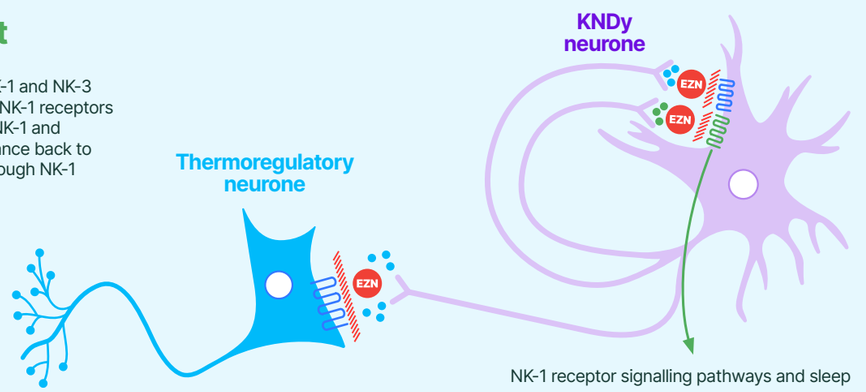
KNDy Neurone Hyperactivity



Dysregulation of thermoregulatory (NK-3) and NK-1 receptor signalling pathways results in hot flashes and sleep disturbances.[8]

NKT for VMS Treatment

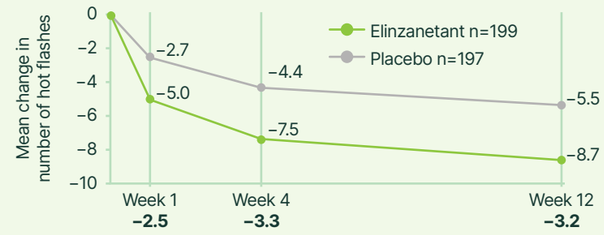
Latest science indicates that by targeting NK-1 and NK-3 receptors centrally in the hypothalamus and NK-1 receptors peripherally in the skin, elinzanetant, a dual NK-1 and NK-3 receptor antagonist, helps to bring balance back to temperature regulation, supporting sleep through NK-1 receptor signalling pathways.[12-14]



Efficacy and Safety of Elinzanetant Has Been Established in a Robust Phase III Clinical Programme[9,12-14]

- Clinical study programme OASIS 1-4 included 1,900 women with moderate-to-severe VMS
- Conducted in 25 countries, spanning a wide-ranging population of diverse and ethnic backgrounds
- Demonstrated efficacy and safety across a diverse range of women, including those with varied smoking histories and a range of BMI

OASIS 1 identified a clinically meaningful reduction in VMS frequency at Weeks 4 and 12[a]



Baseline values: Elinzanetant: 13.4 Placebo: 14.3

Difference in LS mean change from baseline for elinzanetant vs placebo (p<0.001).

[a]Reduction of frequency at Weeks 4 and 12 was the primary study endpoint.

65% reduction in VMS frequency at Week 12 vs **42%** for placebo.[9]

Rapid, **statistically significant reduction in VMS** frequency vs placebo **as early as Week 1**.

OASIS-1 | OASIS-2

Evaluated efficacy and safety in **natural or surgical** postmenopausal women **over 26 weeks**.

OASIS-3

Evaluated **long-term** efficacy and safety in **natural or surgical** postmenopausal women **over 52 weeks**.

OASIS-4

Evaluated efficacy and safety in **women receiving AET for HR+ breast cancer over 52 weeks**.

Key Learnings:

Up to 80% of women experience VMS, with up to 40% experiencing moderate-to-severe symptoms that can significantly affect daily life, sleep, mood, and cognitive function; and yet, many women go untreated.[1-7]

KNDy neurones, located in the hypothalamus, play a role in thermoregulation and sleep, and have become the target of novel VMS therapies.[9-12,15]

Elinzanetant is a dual NK-1 and NK-3 receptor antagonist, offering a much-needed treatment option for women experiencing VMS and has additionally demonstrated improvements in sleep disturbances (a secondary study endpoint), with a favourable safety profile across clinical trials.[12-14]

Elinzanetant was associated with significant and rapid reductions of VMS frequency as early as week 1, which persisted into weeks 4 and 12 and improvements were sustained throughout the study period.[9,12,13]

References

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Abbreviations

AET: adjuvant endocrine therapy; HR+: hormone receptor-positive; KNDy: kisspeptin/neurokinin B/dynorphin; LS: least squares; NK: neurokinin; NKB: neurokinin B; NKT: neurokinin targeted therapy; SP: substance P; VMS: vasomotor symptoms; vs: versus.