Scanning the horizon of pharmacological treatments for women experiencing vasomotor symptoms during menopause: What's new in 2022?

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Recorded following the 2022 North American Menopause Society (NAMS) Annual Meeting (12–15 October 2022) and the International Menopause Society (IMS) 18th World Congress on Menopause (26–29 October 2022)

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Overview

- **Part 1:** Hormone therapy for VMS associated with menopause
- **Part 2:** Non-hormonal therapy for VMS associated with menopause

2022 NAMS Annual Meeting and the IMS 18th World Congress on Menopause

Hormone therapy for VMS associated with menopause

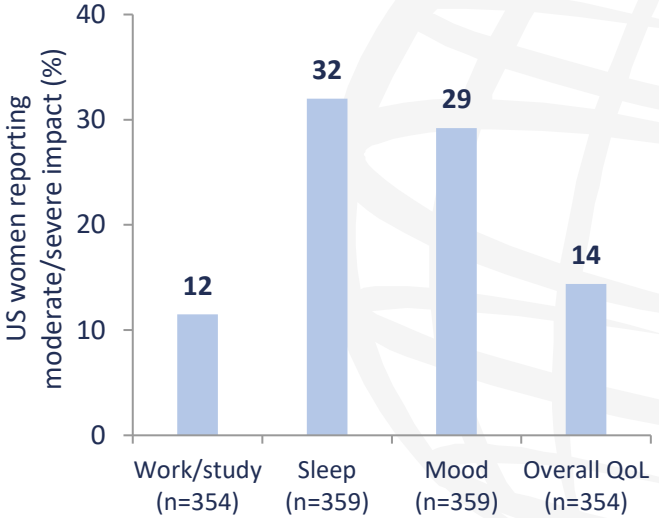
The burden of VMS associated with menopause

Experienced by up to 75% of women[1–3]

Often the most challenging symptoms of menopause:[2,3]

- Hot flashes
- Palpitations
- Night sweats
- Migraine

Moderate/severe impact on daily life[4]



Expert opinion suggests only 25% of patients seek treatment for VMS[5]

QoL, quality of life; VMS, vasomotor symptoms.

1. Nappi RE, et al. *Menopause*. 2021;28:875–82; 2. Peacock K, Ketvertis KM. Menopause. In: StatPearls Publishing. 2022:29939603; 3. Zouboulis CC, et al. *Climacteric.* 2022;25:434–42; 4. Stute P, et al. *Maturitas.* 2022;164:38–45; 5. Reed SD. Presented at: 2022 NAMS Annual Meeting, Atlanta, GA, USA. 12–15 October 2022.

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The 2022 HT position statement of the NAMS[1,2]

- HT is the **most effective treatment for VMS** and can prevent bone loss and fracture
- Treatment should be **individualized** to **maximize benefits** and **minimize risks**
- For women **<60 years** or **≤10 years of menopause onset**, the **benefit–risk ratio of HT = favourable** for treating VMS and bone loss prevention
- For women **>60 years** or **>10 years of menopause onset**, the **benefit–risk ratio of HT = less favourable** (greater risks of CHD, stroke, VTE, dementia)

Not all HTs are the same; risks differ depending on:

- Type
- Dose
- Duration of use
- Administration route
- Timing of initiation
- Progestogen use

CHD, coronary heart disease; HT, hormone therapy; NAMS, North American Menopause Society; VMS, vasomotor symptoms; VTE, venous thromboembolism.

1. The 2022 Hormone Therapy Position Statement of The North American Menopause Society Advisory Panel. *Menopause*. 2022;29:767–94;
2. Faubion S. Presented at: 2022 NAMS Annual Meeting, Atlanta, GA, USA. 12–15 October 2022. Opening Symposium.

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FDA approved oral and transdermal HT[1]

	Estrogen only	Progesterone/ progestin	Estrogen and progesterone/progestin combinations	Estrogen and other hormone combinations
Oral 	Synthetic conjugated estrogens; esterified estrogen	Micronized progesterone; MPA	Estradiol/norethindrone acetate; estradiol/drospirenone; estradiol/norgestimate; estradiol/progesterone; CEE/MPA	Conjugated estrogen/ bazedoxifene
Transdermal 	Estradiol valerate (injection)		Estradiol/ levonorgestrel	
Oral or transdermal 	Estradiol; estradiol acetate; estropipate		Estradiol/ norethindrone acetate	

CEE, conjugated equine estrogen; FDA, US Food and Drug Administration; HT, hormone therapy; MPA, medroxyprogesterone acetate.

FDA. Menopause: Medicines to help you. Available at: https://bit.ly/3SFpjpr (accessed 28 November 2022).

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Oral E2/P4 vs CEE/MPA: Real-world data

Archer DF, et al.[1] Panay N, et al.[2]

- Retrospective, non-interventional real-world analysis of US claims data[1,2]
- VTE risk with two oral HTs for moderate-to-severe VMS[1,2]

N=36,061

- Women aged ≥40 years[1,2]
- No VTE diagnosis 6 months prior to treatment[1,2]

- Oral 1 mg E2/100 mg P4 or CEE/MPA[1,2]
- Treated between April 2019 and June 2021[2]

Primary outcome[1]

- First diagnosis of VTE observed post-index date*

- VTE risk assessed from index date* until switch to comparator or end of follow-up†[1,2]
- Confounding control achieved via IPTW[1,2]

*Index date is the first prescription date. †Follow-up defined as the end of any observed clinical activity or end of data availability.
CEE, conjugated equine estrogen; E2, 17β-estradiol; HT, hormone therapy; IMS, International Menopause Society; IPTW; inverse probability of treatment weighting; MPA, medroxyprogesterone acetate; NAMS, North American Menopause Society; P4, progesterone; VMS, vasomotor symptoms; VTE, venous thromboembolism.

1. Archer DF, et al. Presented at: 2022 NAMS Annual Meeting, Atlanta, GA, USA. 12–15 October 2022. Abstr S-10; 2. Panay N, et al. Presented at: The IMS 18th World Congress of Menopause, Lisbon, Portugal. 26–29 October 2022.

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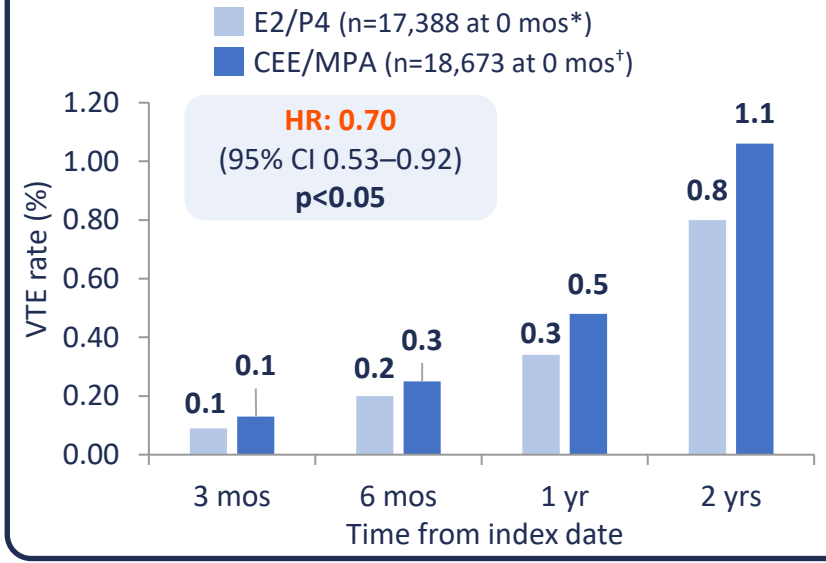
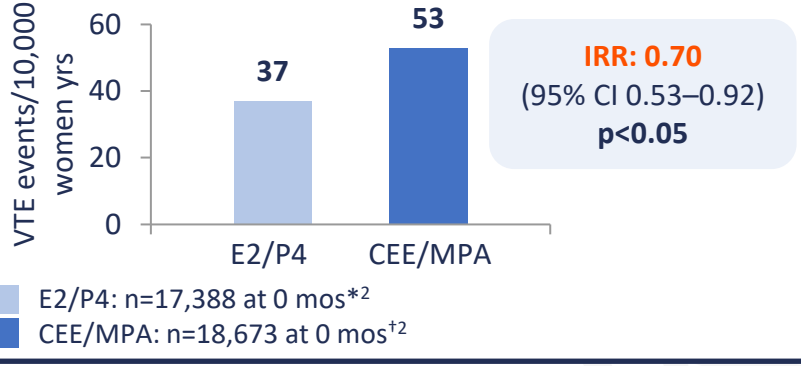
Oral E2/P4 vs CEE/MPA: Real-world data

Archer DF, et al.[1] Panay N, et al.[2]

VTE rates (KM-based) post-IPTW[1,2]



VTE incidence post-IPTW from index date to end of follow-up‡[1,2]



VTE risk significantly lower with E2/P4 vs CEE/MPA, but further research is required to confirm these exploratory analyses

*n=2,116 at 24 mos; †n=2,998 at 24 mos; ‡Follow-up defined as the earliest time point between treatment switch, data cut-off date or end of medical- or pharmacy-based clinical activity. Mean follow-up: 1.2 and 1.4 years post-index for E2/P4 and CEE/MPA, respectively.

CEE, conjugated equine estrogen; CI, confidence interval; E2, 17β-estradiol; HR, hazard ratio; IMS, International Menopause Society; IPTW, inverse probability of treatment weighting; IRR, incidence rate ratio; KM, Kaplan–Meier; mos, months; MPA, medroxyprogesterone acetate; NAMS, North American Menopause Society; P4, progesterone; VTE, venous thromboembolism; yr, year.

1. Archer DF, et al. Presented at: 2022 NAMS Annual Meeting, Atlanta, GA, USA. 12–15 October 2022. Abstr S-10; 2. Panay N, et al. Presented at: The IMS 18th World Congress of Menopause, Lisbon, Portugal. 26–29 October 2022.

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Oral estradiol (E2): Clinical trial data

Ensrud K, et al.

- MsFLASH 03: Randomized, double-blind trial[1,2]
- Quantify changes in serum E1 and E2 concentrations and impact on VMS frequency with E2 vs PBO[1,2]

N=171[1]

- Peri- or post-menopausal women aged 40–62 years[1,2]

- Low dose (0.5 mg) oral E2 QD for 8 weeks;[1,2] then 10 mg MPA QD for 2 weeks[2] **or**
- Oral venlafaxine 37.5 mg QD for 7 days; then 75 mg QD for 7 weeks[2] **or**
- PBO[1,2]

Primary outcome[1]

- Serum E1 and E2 concentrations and VMS frequency with E2 vs PBO

- Serum E1 and E2 levels measured at baseline and 8 weeks[1]
- Multiple linear regression analysis used to assess impact of E1 and E2 levels on VMS frequency[1]

E1, estrone; E2, 17β-estradiol; MPA, medroxyprogesterone acetate; NAMS, North American Menopause Society; PBO, placebo; QD, once daily; VMS, vasomotor symptoms.

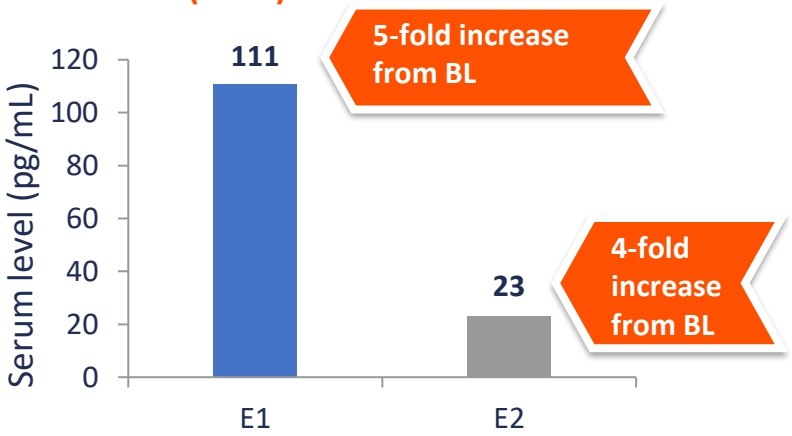
1. Ensrud K, et al. Presented at: 2022 NAMS Annual Meeting, Atlanta, GA, USA. 12–15 October 2022. Abstr S-9; 2. Clinicaltrials.gov. NCT01418209. Available at: https://bit.ly/3N5r7Hc (accessed 28 November 2022).

Oral estradiol (E2): Clinical trial data

Ensrud K, et al.

Serum E1 and E2 levels at week 8

Low-dose E2 (n=72)

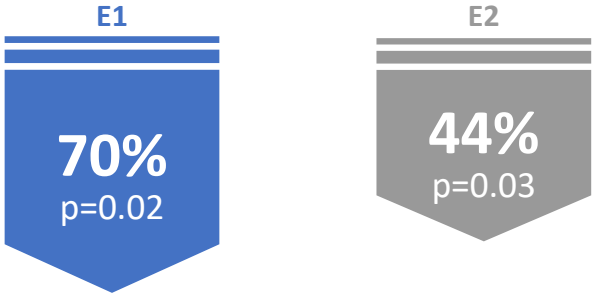


PBO (n=99)

- E1 and E2 levels unchanged from BL

Predicted reduction in VMS frequency with low-dose E2 vs PBO with change in E1 and E2 levels at week 8

(multiple linear regression analysis*)



Increased serum E1 and E2 following low-dose E2 treatment may, in part, mediate effects of HT on reducing VMS

*Performed with treatment assignment and with change in estrogen concentration added to treatment assignment in a regression model predicting VMS frequency at week 8.

BL, baseline; E1, estrone; E2, 17β-estradiol; HT, hormone therapy; NAMS, North American Menopause Society; PBO, placebo; VMS, vasomotor symptoms.

Ensrud K, et al. Presented at: 2022 NAMS Annual Meeting, Atlanta, GA, USA. 12–15 October 2022. Abstr S-9.

E2 transdermal patch vs gel: Clinical trial data

Piette P, et al.

- Randomized, dose-ranging, active-control, multicentre, double-blind, phase III study
- Efficacy and safety of E2 transdermal patch vs gel for moderate-to-severe VMS

N=361

- Postmenopausal women
- ≥7 moderate-to-severe hot flashes daily or ≥60 weekly

Treatment for 3 months with:
- E2 gel (0.06%) 0.625 g, 1.25 g or 2.5 g QD **or**
- E2 transdermal patch 0.05 mg/d QW

Primary outcome
- Frequency and severity of VMS

- Serum concentration–effect relationship, safety (AE incidence) and compliance were also evaluated

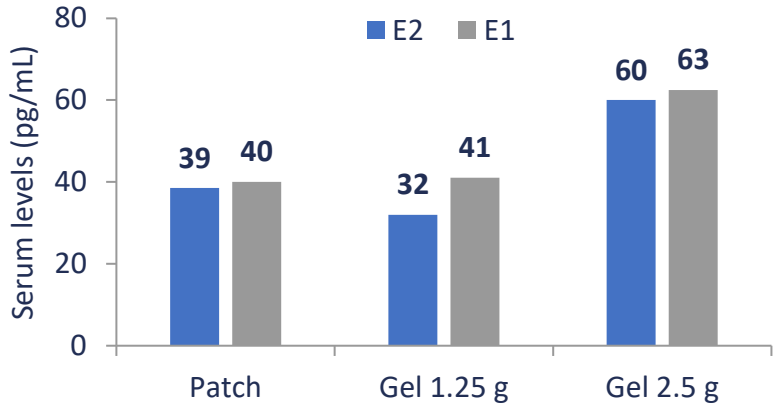
AE, adverse event; E2, 17β-estradiol; IMS, International Menopause Society; QD, once daily; QW, once weekly; VMS, vasomotor symptoms.

Piette P, et al. Presented at: The IMS 18th World Congress of Menopause, Lisbon, Portugal. 26–29 October 2022.

E2 transdermal patch vs gel: Clinical trial data

Piette P, et al.

Median serum E2 and E1 levels at week 12



	Patch	Gel 1.25 g	Gel 2.5 g
Clinical responders at week 12*, % (n/N)	**38% (33/86)**	**26% (23/90)**	**31% (26/84)**

Safety

- Lower proportion of patients reporting application site reactions with gel vs patch (1% vs 21%)

E2 gel was effective in reducing frequency and severity of moderate-to-severe VMS and comparable with patch. These data supported FDA approval of estradiol gel.

*Clinical responders defined as patients who reported no hot flashes at a specified time point. Data reported from two phase III trials.
E1, estrone; E2, 17β-estradiol; FDA, Food and Drug Administration; IMS, International Menopause Society; VMS, vasomotor symptoms.
Piette P, et al. Presented at: The IMS 18th World Congress of Menopause, Lisbon, Portugal. 26–29 October 2022.

Oral estetrol (E4): Clinical trial data

Utian WH, et al.

- E4Comfort I: Phase III randomized open-label trial in Europe, Latin America, US and Canada[1–3]
- E4 vs PBO for moderate-to-severe VMS[1–3]

N=640[1]

- H or NH* post-menopausal women aged 40–65 years[1–3]
- ≥7 daily or ≥50 moderate-to-severe VMS in the week before randomization[1–3]

Randomized 1:1:1 for 12 weeks:[1–3]
- H women: 15 mg E4 : 20 mg E4 : PBO QD
- NH women: +100 mg P4 QD for 14 days after E4/PBO

Co-primary endpoints
- Frequency and severity of VMS at weeks 4 and 12[1–3]

Secondary endpoints[1–3]
- VMS frequency responder analysis
- Safety with ≤12 weeks' treatment

Top-line efficacy and safety results[1]

*For NH women, uterus with bi-layer endometrial thickness ≤4 mm on transvaginal ultrasound.
E4, estetrol; H, hysterectomized; IMS, International Menopause Society; NAMS, North American Menopause Society; NH, non-hysterectomized; P4, progesterone; PBO, placebo; QD, once daily; VMS, vasomotor symptoms.

1. Utian WH, et al. Presented at: The IMS 18th World Congress of Menopause, Lisbon, Portugal. 26–29 October 2022; 2. Utian WH, et al. Presented at: 2022 NAMS Annual Meeting, Atlanta, GA, USA. 12–15 October 2022. Abstr S-13; 3. Clinicaltrials.gov. NCT04209543. Available at: https://bit.ly/3h8Y4qf (accessed 28 November 2022).

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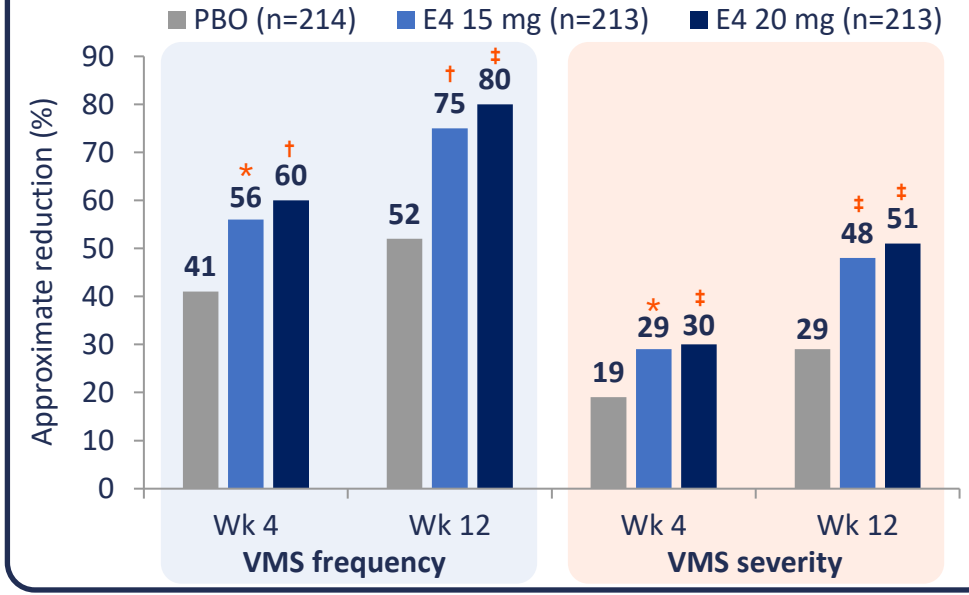
Oral estetrol (E4): Clinical trial data

Utian WH, et al.

Reduction in VMS frequency and severity at weeks 4 and 12[1]



Safety[1]

TEAEs

- Mostly in the reproductive system and breast; mild/moderate
- No major CV or thrombotic events

Endometrium-related TEAEs (NH women)

- Vaginal haemorrhage,[§] endometrial disorder,[‖] thickening[¶] and hyperplasia more frequent in E4-treated NH group vs PBO
  - Data confirmed E4 estrogenic profile and need for progestin in NH women

E4 is a novel emerging HT, well-tolerated and efficacious for the treatment of VMS[1,2]

*p<0.05 vs PBO; †p<0.0005 vs PBO; ‡p<0.0001 vs PBO; §Includes vaginal bleeding and spotting; ‖Includes proliferative and disordered proliferative endometrium; ¶Mean endometrial thickening returned to <4 mm after treatment with P4 200 mg for 2 weeks.

CV, cardiovascular; E4, estetrol; HT, hormone therapy; IMS, International Menopause Society; NAMS, North American Menopause Society; NH, non-hysterectomized; P4, progesterone; PBO, placebo; TEAEs, treatment emergent adverse events; VMS, vasomotor symptoms; wk, week.

1. Utian WH, et al. Presented at: The IMS 18th World Congress of Menopause, Lisbon, Portugal. 26–29 October 2022; 2. Utian WH, et al. Presented at: 2022 NAMS Annual Meeting, Atlanta, GA, USA. 12–15 October 2022. Abstr S-13.

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Conclusions

- **RWE:** E2/P4 associated with lower risk of VTE vs CEE/MPA, but further studies required
- **MsFLASH03 RCT:** Increased serum E1 and E2 levels following low-dose E2 treatment may mediate effects of HT on reducing VMS
- **Pivotal phase III data:** E2 gel effective in reducing frequency/severity of moderate-to-severe VMS and comparable with transdermal patch
- **E4Comfort I trial:** E4, a novel, emerging natural estrogen, reduced frequency/severity of VMS with a favourable safety profile

CEE, conjugated equine estrogen; E1, estrone; E2, 17β-estradiol; E4, estetrol; HT, hormone therapy; MPA, medroxyprogesterone acetate; P4, progesterone; RCT, randomized controlled trial; RWE, real-world evidence; VMS, vasomotor symptoms; VTE, venous thromboembolism.

2022 NAMS Annual Meeting and the IMS 18th World Congress on Menopause

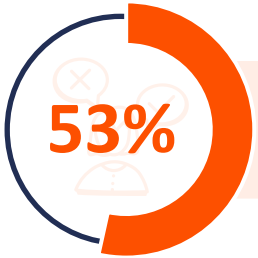
Non-hormonal therapy for VMS associated with menopause

Rationale behind non-hormonal therapy for VMS

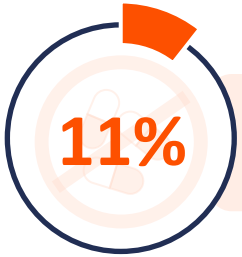
Non-hormonal therapies are suitable for:[1]

- Mild-to-moderate hot flashes or for shorter treatment periods
- Women who are against using HT or would prefer not to
- Women with contraindications to HT (e.g. estrogen-responsive cancers, liver disease)

In a US-based population of women with VMS:[2]



Eligible for HT but against using it



Contraindications preventing HT use

HT, hormone therapy; VMS, vasomotor symptoms.

1. Reed SD. Presented at: 2022 NAMS Annual Meeting, Atlanta, GA, USA. 12–15 October 2022; 2. Stute P, et al. *Maturitas.* 2022;164:38–45.

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Pharmacological non-hormonal therapies for VMS

Approved

- SSRI[1*]

Emerging

- KNDy-targeting agents[2,3]

Off-label

- SNRIs[4]
- Gabapentinoids[4]
- α-adrenergic agonist[4]

*Paroxetine is the only FDA-approved pharmacological non-hormonal therapy for VMS.

KNDy, kisspeptin/NKB/dynorphin; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; VMS, vasomotor symptoms.

1. FDA. Paroxetine PI. 2021. Available at: https://bit.ly/3StrXP7 (accessed 28 November 2022); 2. ClinicalTrials.gov. Available at: https://bit.ly/3TAbB8C (accessed 28 November 2022); 3. Depypere H, et al. *Expert Opin Investig Drugs*. 2021;30:681–94; 4. Biglia N, et al. *Ecancermedicalscience.* 2019;13:909.

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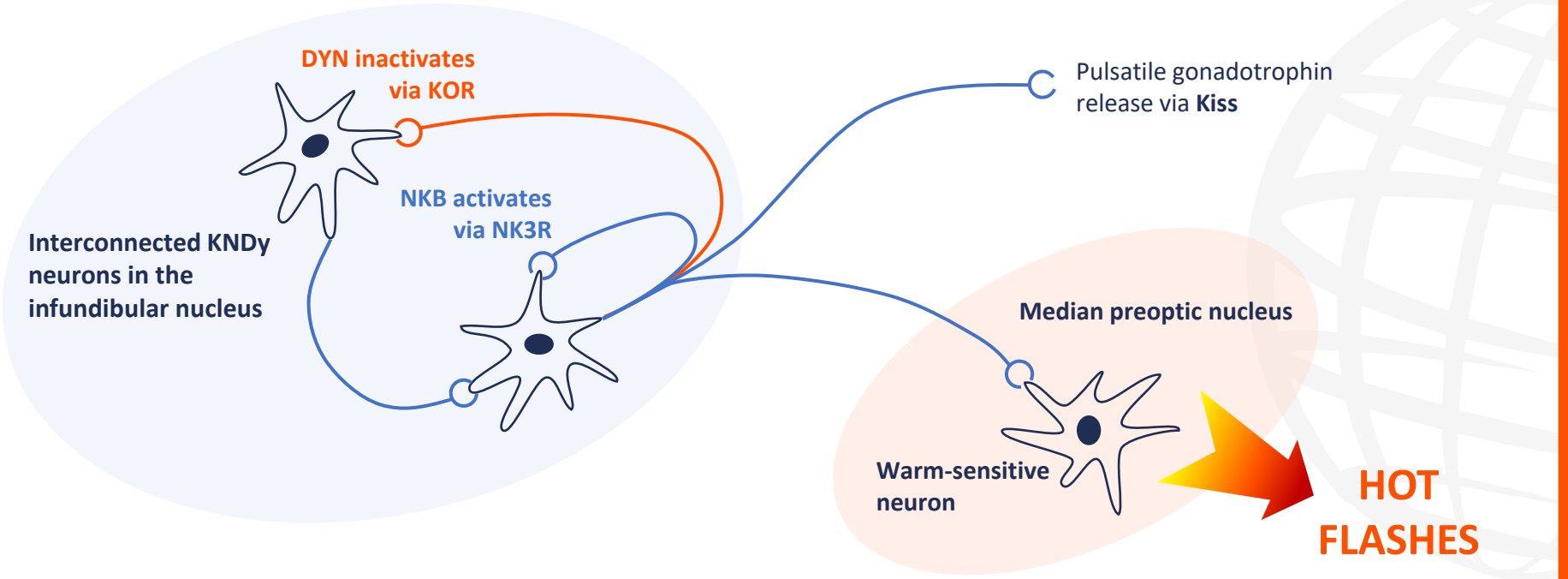
KNDy neurons and thermoregulation[1–3]



DYN, dynorphin; Kiss, kisspeptin; KNDy, kiss-neurokinin B-dynorphin system; KOR, κ-opioid receptor; NK3R, neurokinin 3 receptor; NKB, neurokinin B.

1. Menown SJ, Tello JA. *Adv Ther*. 2021;38:5025–45; 2. Neal-Perry G. Presented at: 2022 NAMS Annual Meeting, Atlanta, GA, USA. 12–15 October 2022; 3. Ruth KS, et al. Presented at: The IMS 18th World Congress of Menopause, Lisbon, Portugal. 26–29 October 2022.

NK3R signalling and VMS

Ruth KS, et al.

- Retrospective, non-interventional GWAS using UK Biobank data
- Hypothesis-free approach to identifying genes

N=92,028

- 14,261 women with VMS
- 77,767 controls

- Statistically test the association between risk of VMS and:
  - Genotype effect at variants using GWAS
  - Carrying predicted loss-of-function alleles using exome analysis

Objective

- To use inherited genetic differences to explore the biology of VMS and inform drug discovery

GWAS, genome-wide association study; IMS, International Menopause Society; NK3R, neurokinin 3 receptor; VMS, vasomotor symptoms.

Ruth KS, et al. Presented at: The IMS 18th World Congress of Menopause, Lisbon, Portugal. 26–29 October 2022.

NK3R signalling and VMS

Ruth KS, et al.

GWAS findings[1]

- **Single genome-wide signal in *TACR3*[1]**
- **OR=0.78** (95% CI 0.74–0.82)[1]

- *TACR3* codes for NK3R[1]
- Replicates findings from previous GWAS meta-analysis[2]
- No strong in silico evidence for functional/biological mechanism[1]

Exome analysis findings[1]

- **LOF *TACR3* variant not significantly associated with VMS[1]**

- LOF *TACR3* variant previously associated with delayed age at menarche[3]
- GWAS signal and LOF variant are independent[1]

Findings support role of *TACR3* in VMS but current understanding of effect on NK3R signalling is limited

CI, confidence interval; GWAS, genome-wide association study; IMS, International Menopause Society; LOF, loss-of-function; NK3R, neurokinin 3 receptor; OR, odds ratio; TACR3, tachykinin receptor 3; VMS, vasomotor symptoms.

1. Ruth KS, et al. Presented at: The IMS 18th World Congress of Menopause, Lisbon, Portugal. 26–29 October 2022; 2. Crandall CJ, et al. *Menopause*. 2017;24:252–61; 3. Lunetta KL, et al. *Nat Commun*. 2015;6:7756.

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Key pharmacological non-hormonal therapies for VMS

Completed phase II and III trials

Phase II

- **Elinzanetant** (SWITCH-1, NCT03596762)
  November 2019
- **Fezolinetant** (NCT05419908)
  September 2016
- **Fezolinetant** (NCT03192176)
  September 2018

Phase III

- **Fezolinetant** (SKYLIGHT 2, NCT04003142)
  July 2020
- **Fezolinetant** (SKYLIGHT 1, NCT04003155)
  October 2020
- **Fezolinetant** (MOONLIGHT 1, NCT04234204)
  April 2022
- **Fezolinetant** (MOONLIGHT 3, NCT04451226)
  June 2022
- **Fezolinetant** (SKYLIGHT 4, NCT04003389)
  January 2022

Dates given are primary completion dates per ClinicalTrials.gov.
VMS, vasomotor symptoms.
All trials can be accessed using their respective NCT number at: https://bit.ly/3TAbB8C (accessed 28 November 2022).

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Key pharmacological non-hormonal therapies for VMS

Ongoing phase II and III trials

Phase II

- **Citalopram +/- gabapentin + a digital CBT program + support person** (MACS, NCT04766229) November 2022
- **Fezolinetant** (STARLIGHT, NCT05034042) November 2022

Phase III

- **Elinzanetant** (OASIS-1, NCT05042362) June 2023
- **Elinzanetant** (OASIS-2, NCT05099159) June 2023
- **Elinzanetant** (OASIS-3, NCT05030584) March 2023
- **Fezolinetant** (DAYLIGHT, NCT05033886) May 2023

Dates given are primary completion dates per ClinicalTrials.gov.
CBT, cognitive behavioural therapy; VMS, vasomotor symptoms.
All trials can be accessed using their respective NCT number at: https://bit.ly/3TAbB8C (accessed 28 November 2022).

Fezolinetant: Clinical trial data (SKYLIGHT 1 and 2)

Nappi R, et al.

- SKYLIGHT 1 and 2: Phase III, PBO-controlled, double-blind, 12-week trials followed by 40-week non-controlled extensions*[1–3]
- VMS frequency, sleep and QoL with fezolinetant vs PBO over 12 wks[1–3]

N=1,022[1]

- Menopausal women aged 40–65 years[1–3]
- ≥7 moderate-to-severe hot flashes/day or 50–60/week within 10 days prior to randomization[2,3]

- QD treatment for 12 weeks
- Randomized 1:1:1 to:[1]
  - Fezolinetant 30 mg
  - Fezolinetant 45 mg
  - PBO*

Primary endpoints[1–3]

- Frequency and severity of moderate-to-severe VMS at 4 and 12 weeks

Secondary endpoints[1–3]

- PROMIS SD SF 8b scores
- Women with ≥50% and ≥75% reduction in VMS
- MENQoL total score and VMS domain score
- Safety

Pooled analysis of SKYLIGHT 1 and 2 data for VMS frequency, sleep disturbance and QoL[1]

*Those who received PBO during 12-week double-blind treatment period were re-randomized to fezolinetant 30 or 45 mg QD during 40-week non-controlled extension.
IMS, International Menopause Society; MENQoL, Menopause-Specific Quality of Life; PBO, placebo; PROMIS SD SF, Patient-Reported Outcomes Measurement Information System Sleep Disturbance–Short Form; QD, once daily; QoL, quality of life; VMS, vasomotor symptoms.

1. Nappi R, et al. Presented at: The IMS 18th World Congress of Menopause, Lisbon, Portugal. 26–29 October 2022; 2. Clinicaltrials.gov. NCT04003155. Available at: https://bit.ly/3zFie1j (accessed 28 November 2022); 3. Clinicaltrials.gov. NCT04003142. Available at: https://bit.ly/3DB0IfU (accessed 28 November 2022).

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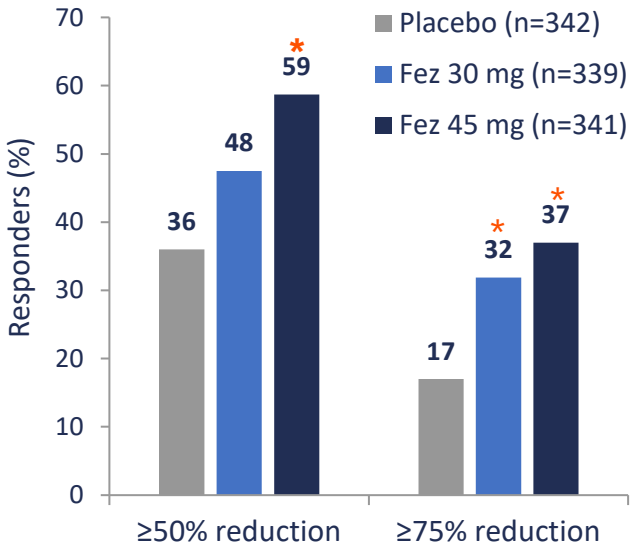
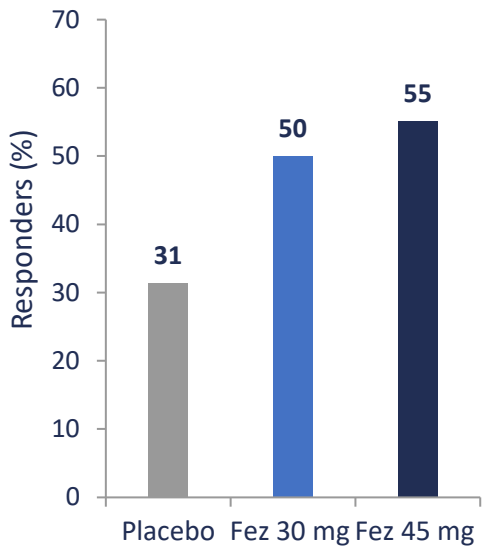
Fezolinetant: Clinical trial data (SKYLIGHT 1 and 2)

Nappi R, et al.

Reduction in VMS frequency at week 12



Clinically meaningful reduction in VMS at week 12



Combined outcomes at week 12

~20% of pts in fez dosing groups vs **~10%** in Placebo group responded to combined outcome measures:

- VMS frequency + PROMIS SD SF 8b total score + MENQoL total score/VMS domain score

Fez was associated with clinically meaningful responses in VMS frequency, sleep and wake function and QoL

*p<0.001 vs PBO.

Fez, fezolinetant; IMS, International Menopause Society; MENQOL, Menopause-Specific Quality of Life; PBO, placebo; PROMIS SD SF, Patient-Reported Outcomes Measurement Information System Sleep Disturbance–Short Form; pts, patients; QoL, quality of life; VMS, vasomotor symptoms.

Nappi R, et al. Presented at: The IMS 18th World Congress of Menopause, Lisbon, Portugal. 26–29 October 2022.

Fezolinetant: Clinical trial data (SKYLIGHT 4)

Neal-Perry G, et al.

- SKYLIGHT 4: Phase III, randomized, double-blind trial[1,2]
- Long-term safety, tolerability and effect on endometrial health of fezolinetant vs PBO[1,2]

N=1,830[1]

- Menopausal women aged 40–65 years seeking treatment for VMS[1,2]
- Randomized 1:1:1 QD for 52 weeks to:[1,2]
  - Fezolinetant 30 mg
  - Fezolinetant 45 mg
  - PBO

Primary endpoints[1,2]

- Endometrial hyperplasia and endometrial cancer incidence ≤1%*
- TEAEs

Secondary endpoints[2]

- Endometrial thickness
- BMD at hip and spine
- TBS at hip and spine
- Safety
- Disordered proliferative endometrium

*To meet the primary endpoints, the rates of hyperplasia or malignancy were to be ≤1% with an upper bound of the one-sided 95% confidence interval ≤4%.
BMD, bone mineral density; NAMS, North American Menopause Society; PBO, placebo; QD, once daily; TBS, trabecular bone score; TEAE, treatment emergent adverse event; VMS, vasomotor symptoms.

1. Neal-Perry G, et al. Presented at: 2022 NAMS Annual Meeting, Atlanta, GA, USA. 12–15 October 2022. Abstr S-11; 2. Clinicaltrials.gov. NCT04003389. Available at: https://bit.ly/3N5JyeP (accessed 28 November 2022).

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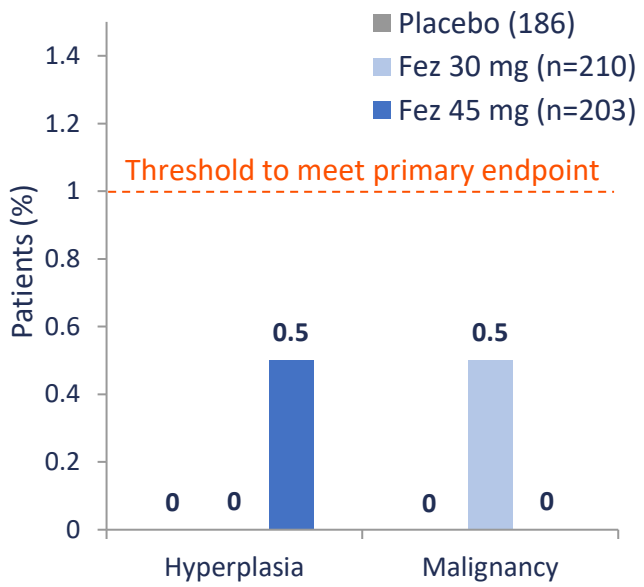
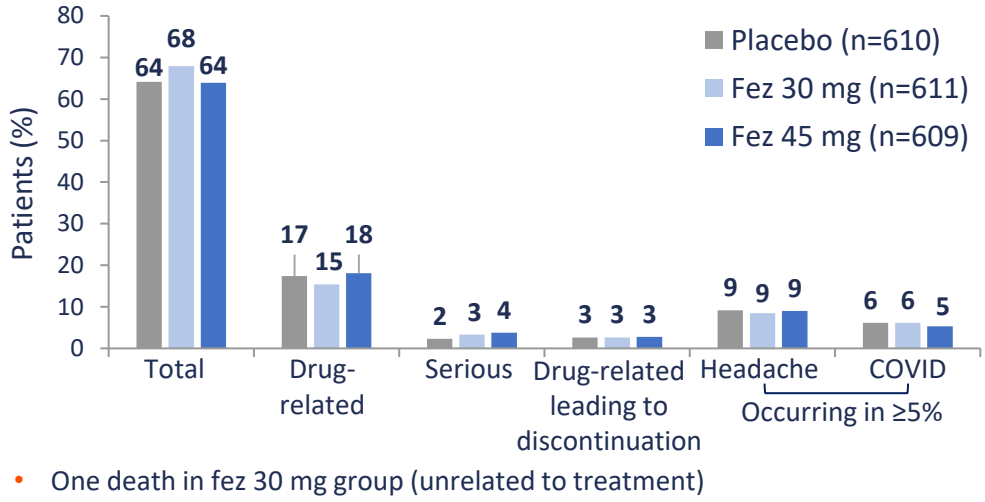
Fezolinetant: Clinical trial data (SKYLIGHT 4)

Neal-Perry G, et al.

Endometrial health*



TEAEs



- One death in fez 30 mg group (unrelated to treatment)

Fez 30 mg and 45 mg met the primary endpoints for endometrial health and was generally well-tolerated

*Prespecified criteria consistent with the appropriate FDA Draft Guidance to Industry must have been met to be included in the primary biopsy data analysis.
Fez, fezolinetant; NAMS, North American Menopause Society; TEAEs, treatment emergent adverse events.
Neal-Perry G, et al. Presented at: 2022 NAMS Annual Meeting, Atlanta, GA, USA. 12–15 October 2022. Abstr S-11.

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Conclusions

- **UK Biobank data analysis:** Supports role of *TACR3* and the NK3R in the genetic basis of VMS, but limited understanding of the effect on NK3R signalling
- **SKYLIGHT 1 and 2 RCTs:** 12-week pooled analyses support efficacy of fezolinetant in reducing VMS frequency, improving functioning and QoL
- **SKYLIGHT 4 RCT:** Primary endpoints met, supporting the safety profile of fezolinetant

NK3R, neurokinin 3 receptor; QoL, quality of life; RCT, randomized controlled trial; TACR3, tachykinin receptor 3; VMS, vasomotor symptoms.

2022 NAMS Annual Meeting and the IMS 18th World Congress on Menopause

Thank you for watching!