Estetrol, the Next Generation of Hormone Therapy: Results of a Phase 2b Dose-finding Study in Postmenopausal Women (E4 Relief)

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Disclosures

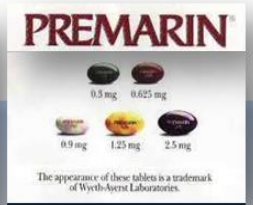
- Mithra USA Advisory Board
- Did not participate in current clinical trials, but has assessed the analyzed data
- Consultant: Mithra, AMAG, Pharmavite, Endoceutics
- Data presented are preliminary and not yet published in a peer reviewed journal

Currently used Estrogens are Aged Molecules

1929
Butenandt and Doisy discover the first estrogen (Estrone)

1930
Estriol

1936
Estradiol



1941
Conjugated Estrogens

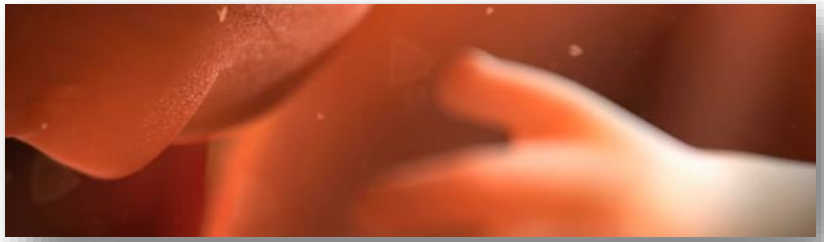
1943
Ethinyl-estradiol

No significant improvement for almost 80 years

Physiology of Estetrol (E4)

Estetrol (E4)

- Is produced by the fetal liver, crosses the placenta, is detected from the 9th week of gestation in maternal urine. Fetal plasma levels are 12 times higher than those of the mother
- Circulates at high concentrations (up to 30 nM) in fetal plasma
- Has a very long half-life (28–32 hours)

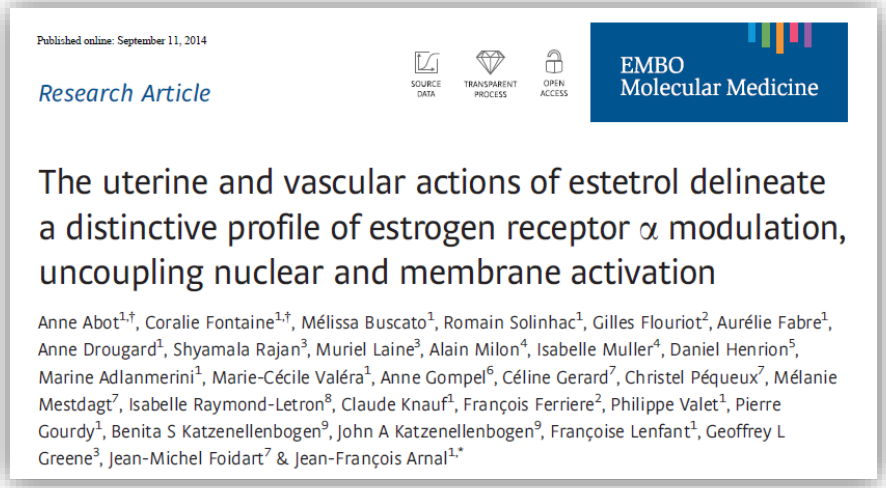


Estetrol (E4) is a NEST

Estetrol (E4) is an estrogen with a distinctive profile of ERα activation

E4 activates the nuclear ERα, but is an antagonist of the membrane ERα

E4 is the first Native Estrogen with Selective Action in Tissues (NEST)



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Research Article

SOURCE DATA | TRANSPARENT PROCESS | OPEN ACCESS

EMBO Molecular Medicine

The uterine and vascular actions of estetrol delineate a distinctive profile of estrogen receptor α modulation, uncoupling nuclear and membrane activation

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Phase 2 Clinical Trial

Multicenter, Dose-Finding, Randomized, Double-Blind, Placebo-Controlled Study to Select the Daily Oral Dose of E4 for the Treatment of Vasomotor Symptoms (VMS) in Post-Menopausal Women

Clinicaltrials.gov NCT0283431 | EudraCT 2015-004018-44

Disposition of Subjects

- Clinical trial conducted in Europe (Belgium, UK, Ireland, Czech Republic, and Poland)
- Mean age: 54.2 ± 4.4 years

			E4			
	Total	Placebo	2.5 mg	5 mg	10 mg	15 mg
Randomized	260	55	54	48	53	50
Treated	257	55	53	47	53	49
Completers	200	41	44	36	38	41
Discontinued	57	14	9	11	15	8

Clinicaltrials.gov NCT0283431 | EudraCT 2015-004018-44

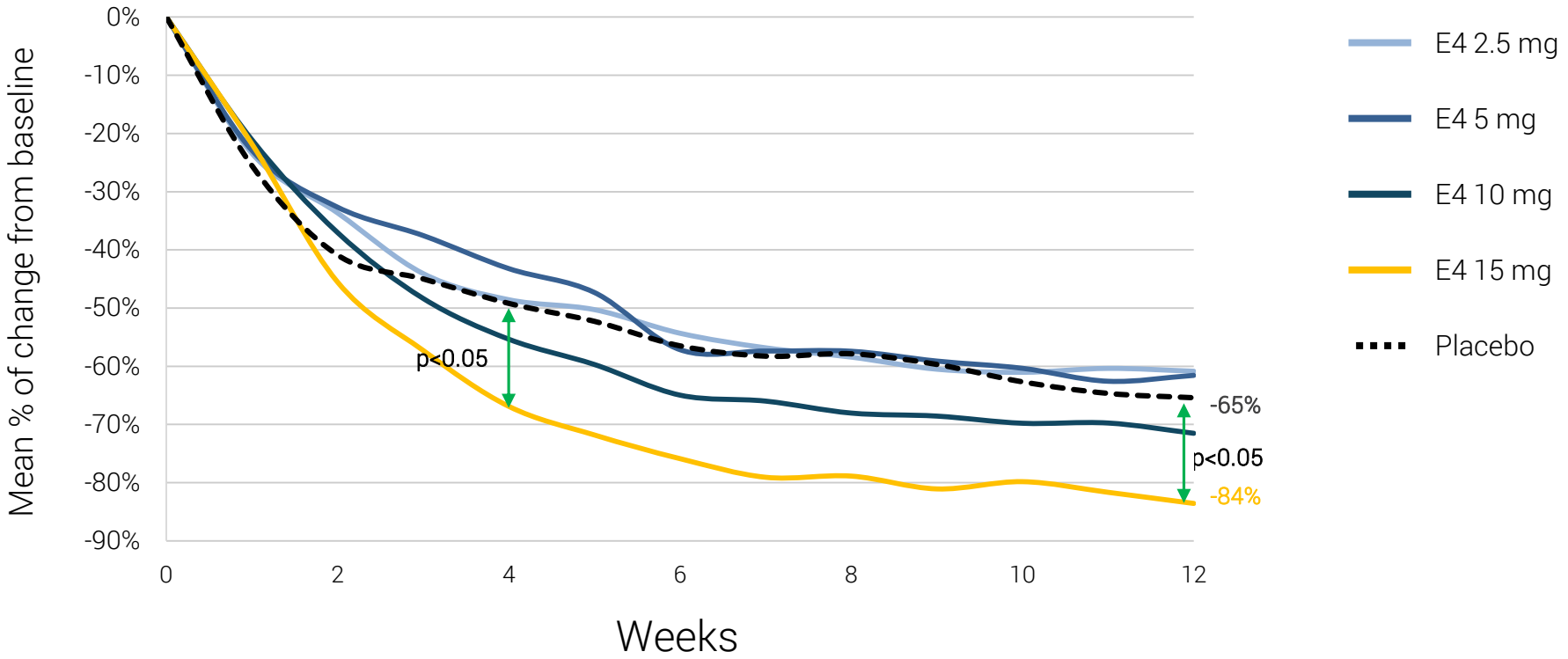
Data on file Mithra Pharmaceuticals

Main Inclusion and Exclusion Criteria

- Written informed consent
- Postmenopausal women
- 40–65 years
- BMI 18–35 kg/m^2
- ≥7 moderate to severe hot flushes per day, or ≥50 moderate to severe hot flushes in the week preceding randomization
- Not hysterectomized if transvaginal ultrasonography (TVUS) showed a bilayer endometrial thickness ≤5 mm

- A history of malignancy, thromboembolism or coagulopathy, diabetes with poor glycemic control, and breast cancer
- Women with a uterus and history or presence of uterine cancer, endometrial hyperplasia, polyp, or abnormal cervical smear

E4 15 mg reduced VMS frequency



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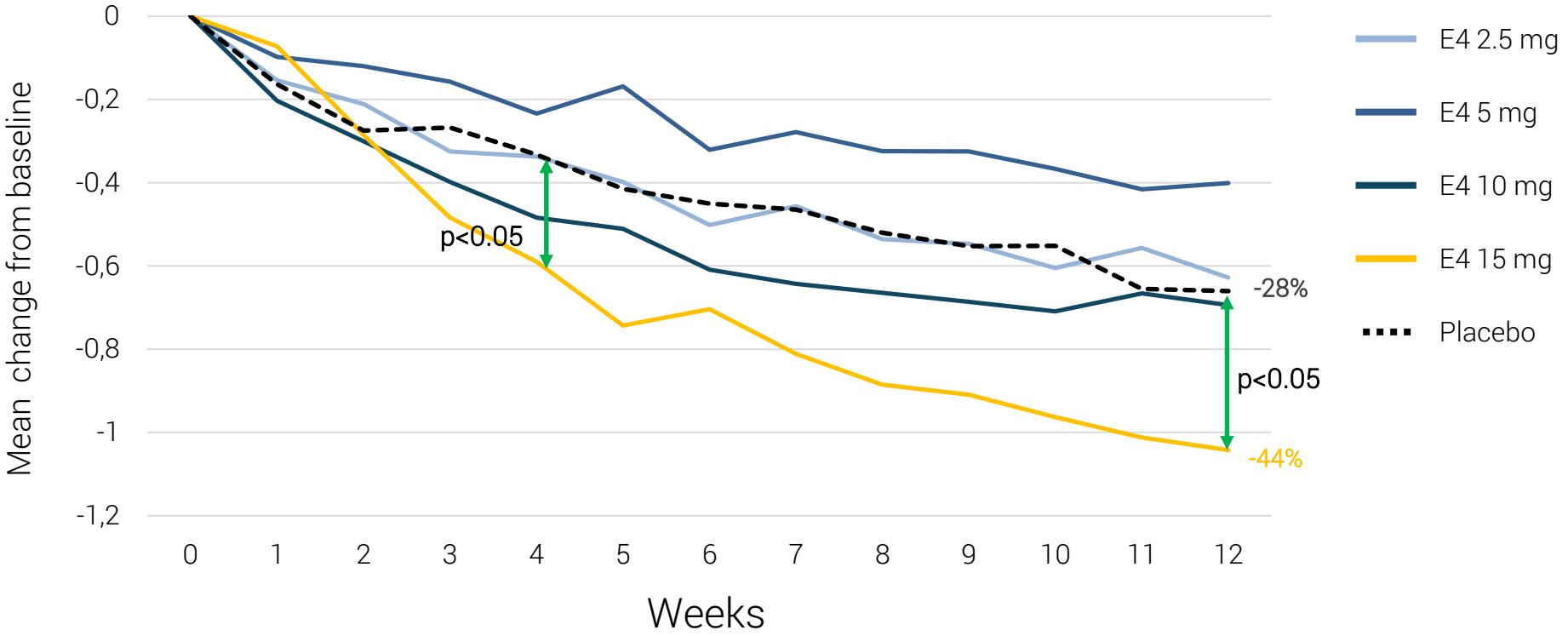
E4 15 mg reduced VMS Severity



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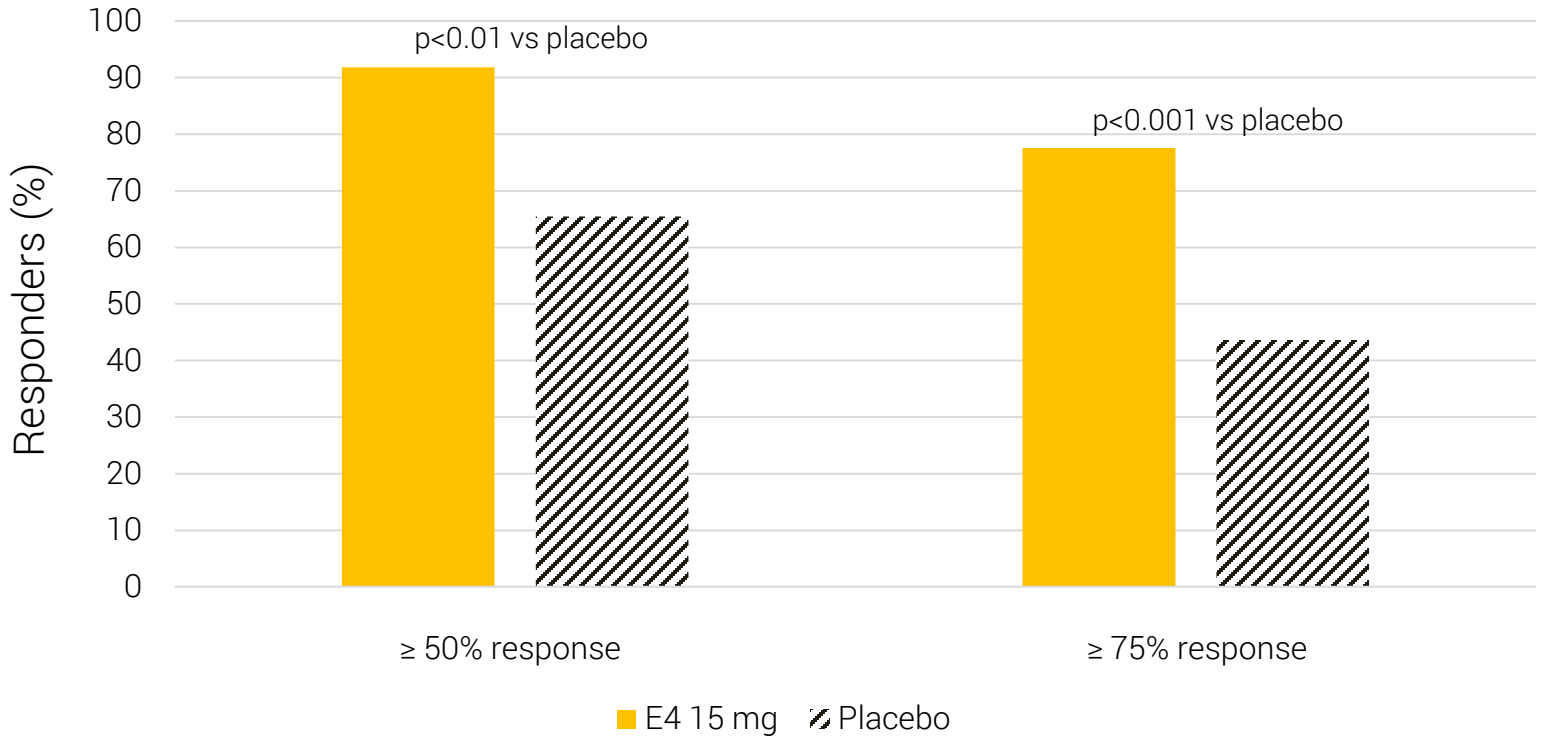
E4 15 mg reduced VMS frequency



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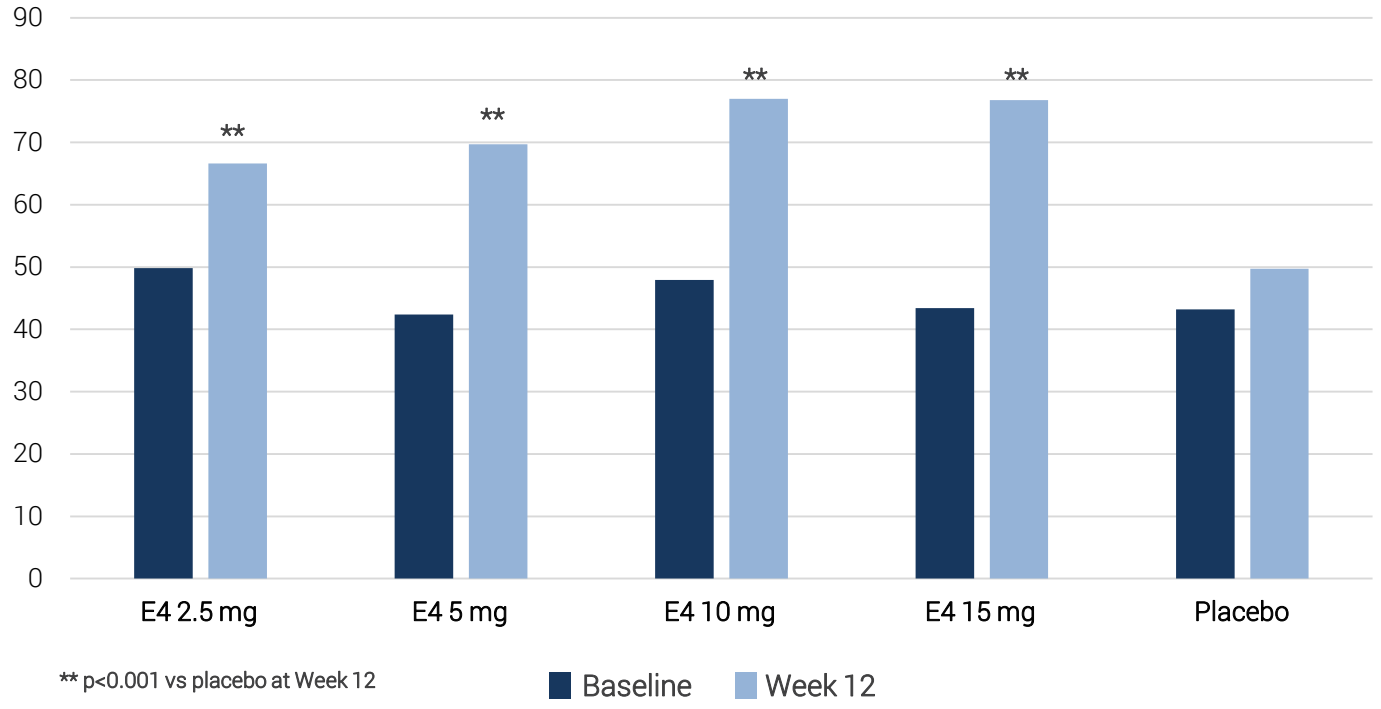
E4 increased the Vaginal Maturation Index



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Changes in all Hemostatic, Lipid, and Glucose Metabolism Markers were within Normal Ranges

E4 did not affect:

1. Any of the coagulation markers (prothrombin fragment 1+2, D-dimer, anti-thrombin, Protein-C, free Protein-S, Factor VIII, and free tissue factor pathway inhibitor).
2. The majority of the lipid and glucose metabolism parameters.

Treatment with E4 resulted in:

1. Small but potential beneficial changes in HDL-C and HbA1c values in the E4 10 mg and E4 15 mg groups.
2. Reduced CTX-1 and osteocalcin values, suggesting reduction in bone resorption.
3. A slight though significant increase in the baseline SHBG concentration in the E4 10 mg and E4 15 mg group, indicating that the E4 estrogenic effect was mild and dose dependent.

Safety

- No endometrial hyperplasia
- In the 15 mg E4 group, the mean endometrial thickness increased from 2 to 6 mm and returned to baseline after progestin therapy
- Well tolerated
- No unexpected adverse events

Summary: Effects of E4

- All doses studied improved GSM/VVA
- 15 mg appears to be minimum effective dose for VMS
- The E4 15 mg dose:
  - Positively influenced bone turnover
  - Did not increase triglyceride levels
  - Increased HDL-C
  - Improved glucose tolerance
  - Had no effects on coagulation parameters
- There were no apparent safety concerns, E4 was well tolerated

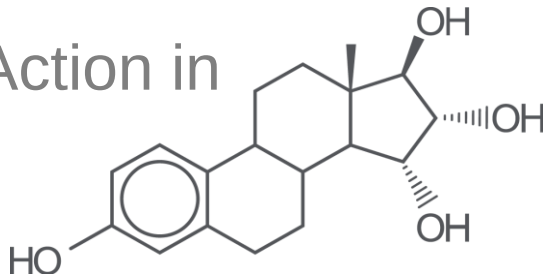
E4 is the First NEST

Native

Estrogen with

Selective Action in

Tissues



- Low risk of drug-drug interactions
- Low breast stimulation, pain, and low carcinogenic impact
- Low impact on triglyceride levels
- Neutral impact on markers of VTE risk

Kluft C et al. Contraception. 2017 Feb;95(2):140-147 | Gerard C et al. Oncotarget. 2015;6(19):17621-36 | Visser M et al. Horm Mol Biol Clin Invest. 2012;9:95-103 | Visser M et al. Climacteric. 2008 11 Suppl 1:64-8
Mawet M et al. Eur J Contracept Reprod Health Care. 2015;20(6):463-75 | Apter D. et al. Contraception. 2016;94(4):366-73 | Data on file Mithra Pharmaceuticals

Conclusion

- E4 is a promising natural estrogen for the treatment of postmenopausal women
- The selective tissue properties create a unique safety profile that should enhance the oral therapeutic utility of E4

Q&A

Low Risk of Drug-drug Interactions

E4 does not interact with the CYP450 family
The risk of drug-drug interactions is low

% inhibition of cytochrome P450 enzymes					
	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4
EE	<10	<10	82	<10	45
E2	19	<10	63	<10	<10
E4	<10	<10	<10	<10	<10

Visser M et al., Climacteric. 2008 1 (suppl 1):31-40

Placebo Effects are expected in the Treatment of Hot Flushes

- In a meta-analysis of 85 menopause trials, significant differences were observed in placebo responses for hot flushes (Li 2017):
  - 5.8% – 71.8% at week 12 (n=8,302)
  - Age, BMI, number of HF at baseline, time since menopause, and route of administration were not related to a placebo response
  - Placebo response was higher in hormonal drug than non-hormonal drug trials
  - Placebo response increased over time and reached a plateau after week 12
- Variability depends on:
  - Type of disorder, severity of symptoms, heterogeneity of trial design, participant characteristics, subjective expectations of clinician and patient (Freeman 2015)

Freeman EW et al. Psychosom Med. 2015 Feb-Mar;77(2):167-75 | Li L et al., Menopause. 2017 Aug;24(8):932-937| Loprinzi CL J Clin Oncol. 2009 Jun 10;27(17):2831-7 | MacLennan AH et al. Cochrane Database Syst Rev. 2004 Oct 18;(4):CD002978.