



Menopausa: Update in tema di TOS

Costantino Di Carlo

22 Settembre 2021

Novità in TOS

Capsule molli contenenti

1 mg estradiolo (come estradiolo emidrato) and 100 mg di progesterone micronizzato.

Status in USA

Approvato ad Ottobre 2018

Lancio Aprile 2019 (Therapeutics MD)

Indicazioni (US Prescribing Information)

Un'associazione di un estrogeno e di progesterone indicata in una donne con utero, per il trattamento di sintomi vasomotori da moderati a gravi dovuti alla menopausa

Status in Europa

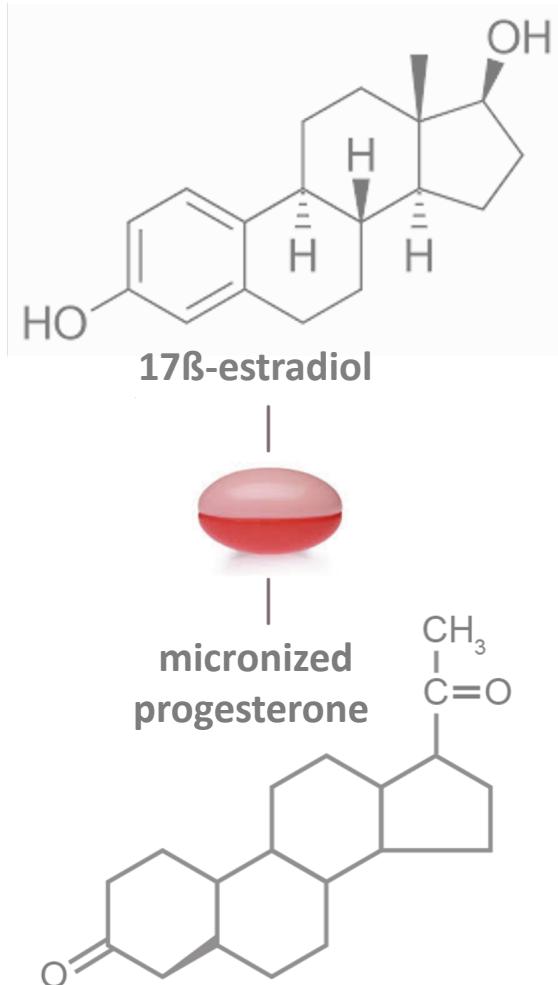
Dossier approvato

Indicazioni (SmPC)

Terapia sostitutiva ormonale combinata continua per i sintomi di deficienza estrogenica in donne in postmenopausa con utero intatto e almeno 12 mesi dopo l'ultima mestruazione. L'esperienza nel trattamento delle donne oltre i 65 anni è limitata.

Associare il 17 β -estradiolo e il progesterone in una sola capsula è tecnicamente molto difficile per le differenti proprietà delle due molecole

Bijuva è il primo farmaco in cui questa associazione è riuscita



Ogni capsula molle contiene

1 mg estradiolo (E2)

+

100 mg progesterone (P4)

Identici agli ormoni endogeni

Google

bioidentical hormones

Cerca

bioidentical hormones

Accedi

Bioidentical Hormones

Used in bioidentical hormone replacement therapy, bioidentical hormones are derived from animal- or plant-based compounds to be molecularly identical to endogenous hormones.

- TYPES**
- BENEFITS**
- POSSIBLE SIDE EFFECTS AND RISKS**
- ALTERNATIVES**

Bioidentical Hormones | Menopause Now
menopausenow.com

Bioidentical Hormones

Bioidentical hormones are plant- or animal-derived hormones that are created in a lab to be identical to endogenous ones.

- COMMON BIODENTICAL HORMONES**
- BIODENTICAL HORMONES AND MENOPAUSE**
- RISKS AND SIDE EFFECTS**
- ALTERNATIVES**

Bioidentical Hormones | SheCares
shecares.com

What Are Bio-Identical Hormones - Yunique M...

Look Great! Feel Great! Lose Weight! Have Better Sex!

L.L. Wright, M.A., C.N.C., M.B.A.

Bioidentical Hormones ...
amazon.it

BIOIDENTICAL Hormones Made Easy!

Look Great! Feel Great! Lose Weight! Have Better Sex!

L.L. Wright, M.A., C.N.C., M.B.A.

What Are the Pros and Cons of Bioidentical Hormones?

Reduced risk of colorectal cancer
Fewer fractures
Check with your doctor before deciding to use bioidentical hormones.
shecares.com

Bioidentical Hormones: Therapy Uses & Side ...

emedicinehealth.com

Is Bio-Identical Hormone Therapy Safe? | Everyd...

everydayhealth.com

5 Reasons You Should Learn to Presc...

bhrtrainingacademy.com

Not All Hormone Replacement Therapies Are Equ...

ht-ca.com

Are bio-identical hormones saf...

cspinet.org

Common Bioidentical Hormones | SheCar...

shecares.com

What Are Bioidentical Hormones? - B...

burtsrx.com

BIOIDENTICAL HORMONE REPLACEMENT THERAPY

Serenity Health Care Center offers BHRT to balance hormones and treat conditions such as Low Libido, Menopause, Low Testosterone, Endometriosis, Hot Flashes, Insomnia and more.

Bioidentical Hormones – Functional Medicine Clinic Near ...
serenityhealthcarecenter.com

Bioidentical Hormone ...

menopause.org.au

HORMONE HANDBOOK

OPTIMIZING YOUR HEALTH THROUGH BIODENTICAL HORMONES

Brannon, MD, FACOG
OPTIMAL BIO

The Hormone Handbo...
amazon.it

BHRT Bioidentical Hormone Replacement Therapy

Bioidentical Hormones Replacement Therapy | My ...
myclinic.com.my

About Bioidentical Hormones

What They Are	What Do They Do	About Bioidentical HRT
<ul style="list-style-type: none"> Also called "natural" hormones Have similar chemical structures to endogenous hormones Made from plant chemicals or animal derivatives 	<ul style="list-style-type: none"> Relieves symptoms of hormonal imbalance, such as: Hot flashes Mood swings Vaginal dryness 	<ul style="list-style-type: none"> HRT that uses bioidentical hormones Prescribed as gels, gels, creams, patches, shots, etc. Not proven safer than traditional HRT

About Bioidentical Hormones | SheCares
shecares.com

Bioidentical Hormones Risks and Side Effects

Risks

- Blood clots
- Strokes
- Heart disease
- Breast cancer

Side Effects

- Mood swings
- Headaches
- Weight gain
- Digestive issues

Pin on Bioidentical hormones
pinterest.com

In Italia, dove la problematica “ormoni bioidentici” non esiste, perché da sempre usiamo l’estradiolo, questa nuova associazione presenta altri aspetti interessanti

Al momento attuale, rappresenta l’unica possibilità di praticare TOS con estradiolo e progesterone naturale per os.

Questo tipo di terapia presenta diversi vantaggi, reali e teorici.

FARMACI PER LA TERAPIA ORMONALE IN POSTMENOPAUSA

Nome	Principio attivo	Regime	Note	
	Estrogeno	Progesterinico		
Terapie cicliche, sequenziali o combinate, orali (con mestruazione)				
	E2 emidrato 1,5 mg	NOMAC 3.75 mg	(10+14) + 4 (sosta)	
	E2 emidrato 1 mg	DDG 10 mg	(14+14) (no sosta)	
	E2 emidrato 2 mg	DDG 10 mg	(14+14) (no sosta)	
	E2 valerato 2 mg	CYP 1 mg	(11+10) + 7 (sosta)	
	E2 valerato 2 mg	MAP 10 mg	(11+10) + 7 (sosta)	
Terapie combinate continue (senza mestruazione)				
	E2 emidrato 1 mg	DRSP 2 mg	continuo	Bloccato
	E2 emidrato 1 mg	NETA 0.5 mg	continuo	
	E2 emidrato 1 mg	DDG 5 mg	continuo	
	E2 valerato 1 mg	DNG 2 mg	continuo	Bloccato
	Tibolone		continuo	

Estrogeni orali

	E2 valerato 2mg		Bloccato
	ECE 0,45 + Bazedoxifene 20 mg		Bloccato

Estrogeni transdermici

	17B estradiolo 25 o 50 mcg/die	2 / settimana	cerotto
	17B estradiolo 50 o 100 mcg/die	2 / settimana	cerotto
	17B estradiolo	3 erogazioni /die	gel
	17B estradiolo	1 bustina /die	gel
	17B estradiolo	1 spray/die	spray cutaneo

Progestinici

	NOMAC 5 mg		
	Progesterone 100 o 200 mg		Per os o per vagina
	DDG 10 mg		
	MAP 5 o 10 o 20 mg		

Changing Concepts: Menopausal Hormone Therapy and Breast Cancer

Rowan T. Chlebowski, Garnet L. Anderson

Manuscript received September 16, 2011; revised December 20, 2011; accepted January 2, 2012.

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Al termine dei 9 anni complessivi (trattamento + osservazione), le pazienti trattate con E + P presentano un rischio di K mammario significativamente superiore ai controlli, mentre quelle trattate con E presentano un rischio significativamente inferiore ai controlli.

Il progestinico (MAP) sembra essere quindi il principale responsabile del rischio oncologico mammario.

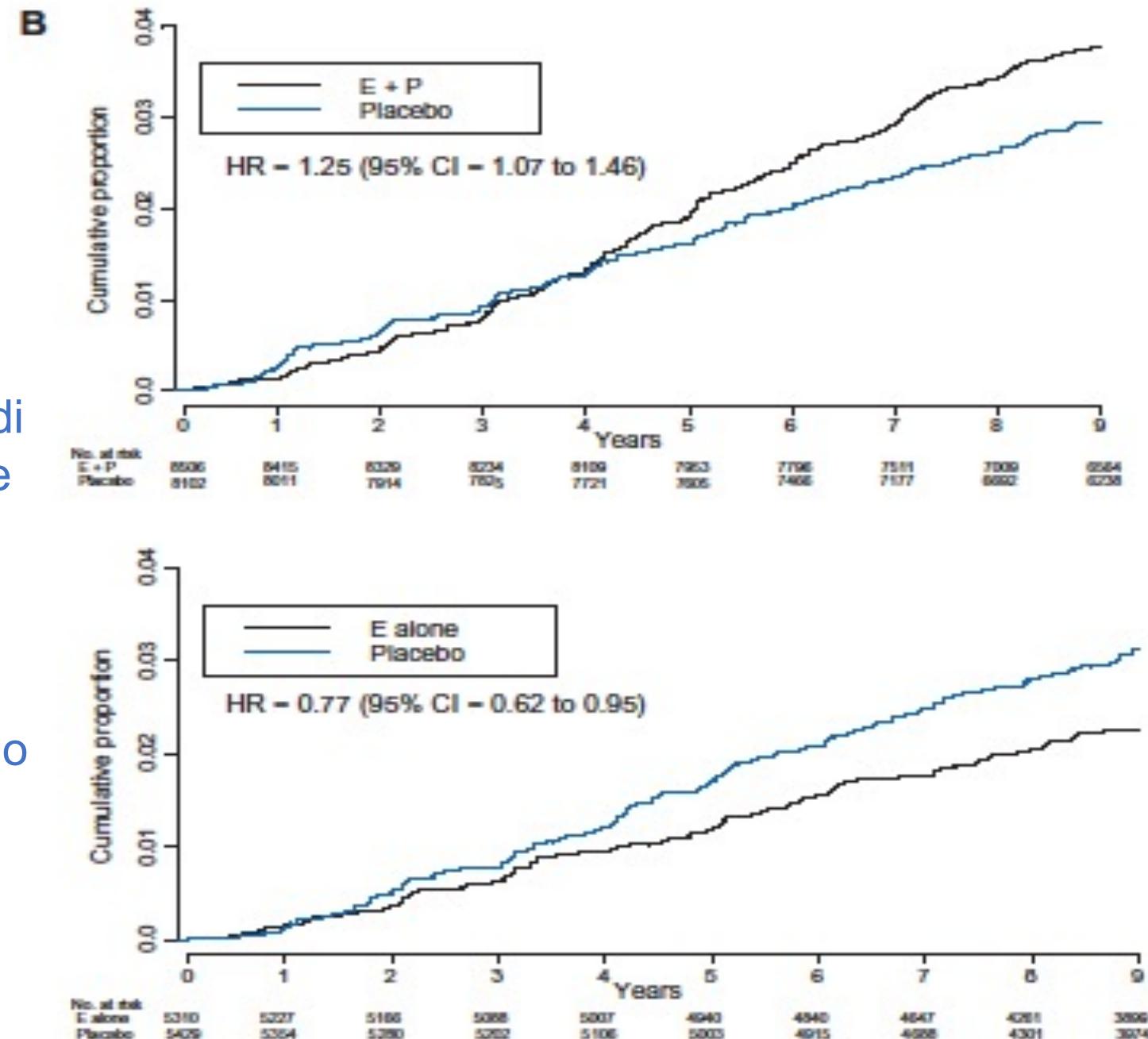


TABLE 6. Risk of breast cancer with hormone therapy containing progesterone or progestins in large observational studies

Study	Estrogen and/or progestogen	HR (95% CI)
Fournier et al, 2014 ⁶	Estrogen alone	1.17 (0.99-1.38)
	Estrogen plus progesterone/dydrogesterone	1.22 (1.11-1.35)
	Estrogen plus synthetic progestins	1.87 (1.71-2.04)
Cordina-Duverger et al, 2013 ⁷	Estrogen alone (any)	1.19 (0.69-2.04)
	Estrogen (any) with progestogens	1.33 (0.92-1.92)
	Natural progesterone	0.80 (0.44-1.43)
	Synthetic progestins	1.72 (1.11-2.65)
	Progesterone derivatives	1.57 (0.99-2.49)
	Testosterone derivatives	3.35 (1.07-10.4)
Fournier et al, 2008 ⁵	Oral estrogen alone	1.32 (0.76-2.29)
	Oral estrogen plus progestogen	
	Progesterone	Not analyzed ^a
	Dydrogesterone	0.77 (0.36-1.62)
	Medrogestone	2.74 (1.42-5.29)
	Chlormadinone acetate	2.02 (1.00-4.06)
	Cyproterone acetate	2.57 (1.81-3.65)
	Promegestone	1.62 (0.94-2.82)
	Nomegestrol acetate	1.10 (0.55-2.21)
	Norethisterone acetate	2.11 (1.56-2.86)
	Medroxyprogesterone acetate	1.48 (1.02-2.16)
	Transdermal estrogen alone	1.28 (0.98-1.69)
	Transdermal estrogen plus progestogen	
	Progesterone	1.08 (0.89-1.31)
	Dydrogesterone	1.18 (0.95-1.48)
	Medrogestone	2.03 (1.39-2.97)
	Chlormadinone acetate	1.48 (1.05-2.09)
	Cyproterone acetate	Not analyzed ^a
	Promegestone	1.52 (1.19-1.96)
	Nomegestrol acetate	1.60 (1.28-2.01)
	Norethisterone acetate	Not analyzed ^a
	Medroxyprogesterone acetate	Not analyzed ^a
Fournier et al, 2005 ⁴	Estrogen alone	1.1 (0.8-1.6)
	Estrogen plus progesterone	0.9 (0.7-1.2)
	Transdermal estrogen	0.9 (0.7-1.2)
	Oral estrogen	No events
	Estrogen plus synthetic progestins	1.4 (1.2-1.7)
	Transdermal estrogen	1.4 (1.2-1.7)
	Oral estrogen	1.5 (1.1-1.9)

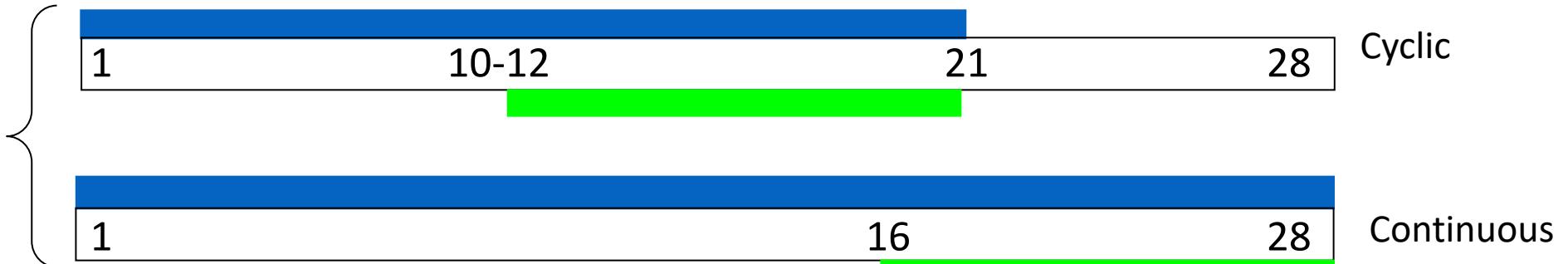
Posologia

Terapia **combinata continua**. Come tale va assunta tutti i giorni: **una capsula alla sera a stomaco pieno**.

La somministrazione serale è importante: alcuni metaboliti del progesterone (specie l'allopregnenolone) hanno un effetto favorevole sui disturbi del sonno modulando la trasmissione GABA-ergica (in modo simile alle benzodiazepine)

HRT schedules

Sequential therapy



Combined therapy



Estrogen

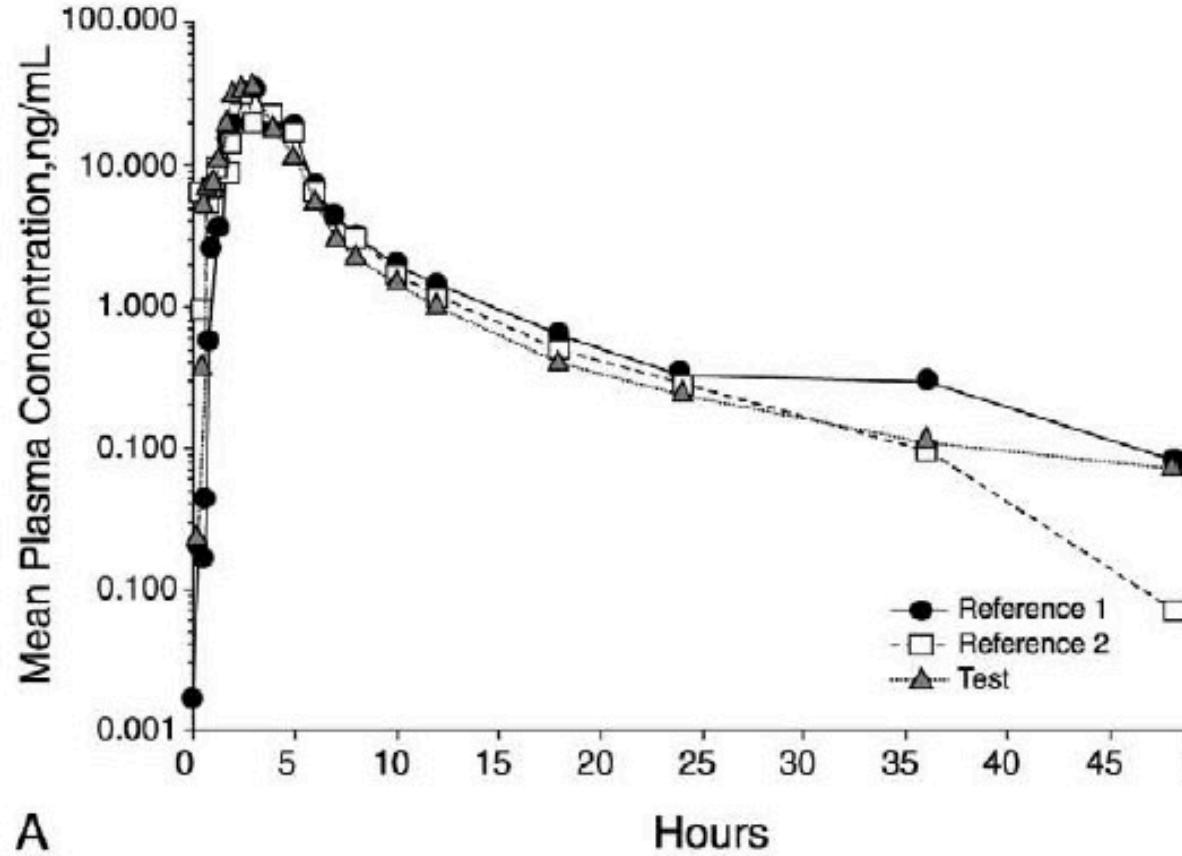


Progestogen

Pharmacokinetics of the first combination 17 β -estradiol/progesterone capsule in clinical development for menopausal hormone therapy

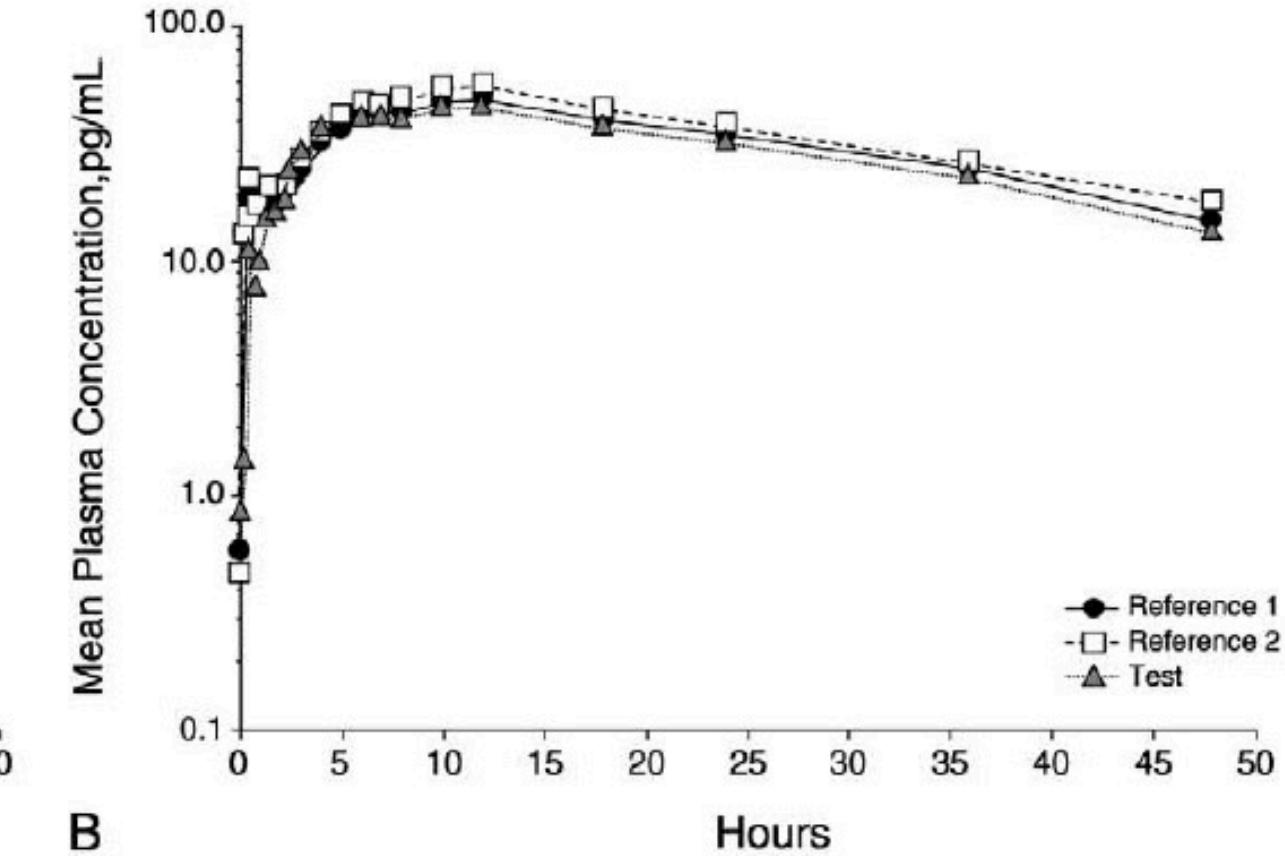
James H. Pickar, MD,¹ Charles Bon, MS,² Julia M. Amadio, MBA,³ Sebastian Mirkin, MD,³ and Brian Bernick, MD³

Progesterone



A

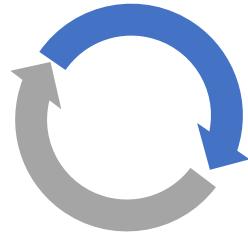
Unconjugated estradiol



B

L'estradiolo e il progesterone associati hanno una farmacocinetica sovrapponibile a quella di estradiolo e progesterone presi insieme ma separatamente

L'efficacia su multipli outcomes e la sicurezza a lungo termine sono state valutate in un ampio RCT



REPLENISH

A phase III, prospective, randomized, double-blind, placebo-controlled, parallel-group, 12-month, multicenter trial evaluating the safety and efficacy of 17 β -estradiol/micronized progesterone oral capsules in postmenopausal women with an intact uterus

REPLENISH: Study design

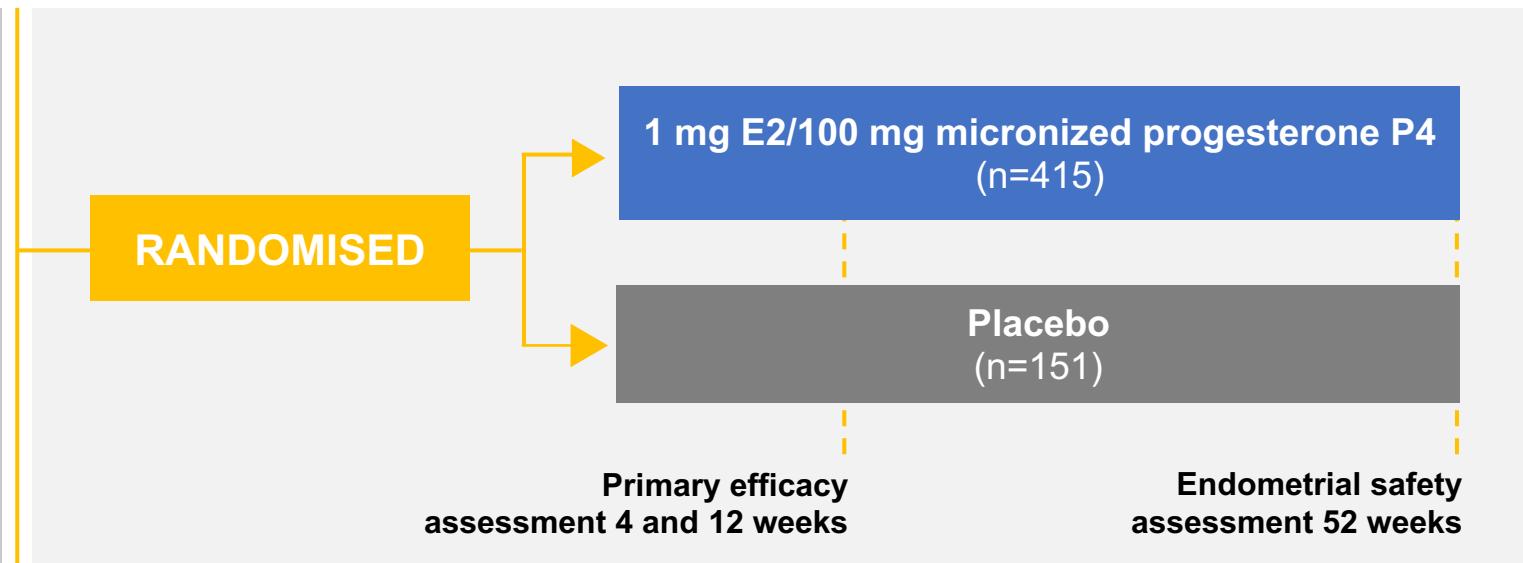
Randomized, double-blind, placebo-controlled, multicenter study
of menopausal women aged **40-65 years** treated for 12 months¹⁻³

Key criteria for inclusion

- ≥7 moderate-to-severe hot flushes per day or ≥50 per week
- intact uterus
- serum estradiol level of ≤50 pg/mL
- body mass index ≤34 kg/m²
- acceptable endometrial biopsy results

Key criteria for exclusion

- contraindication/allergy to estrogen or progesterone therapy
- history of melanoma, breast, uterine or ovarian cancer
- history of thrombosis, coronary artery or cerebrovascular disease
- chronic liver or kidney disease



Primary endpoints

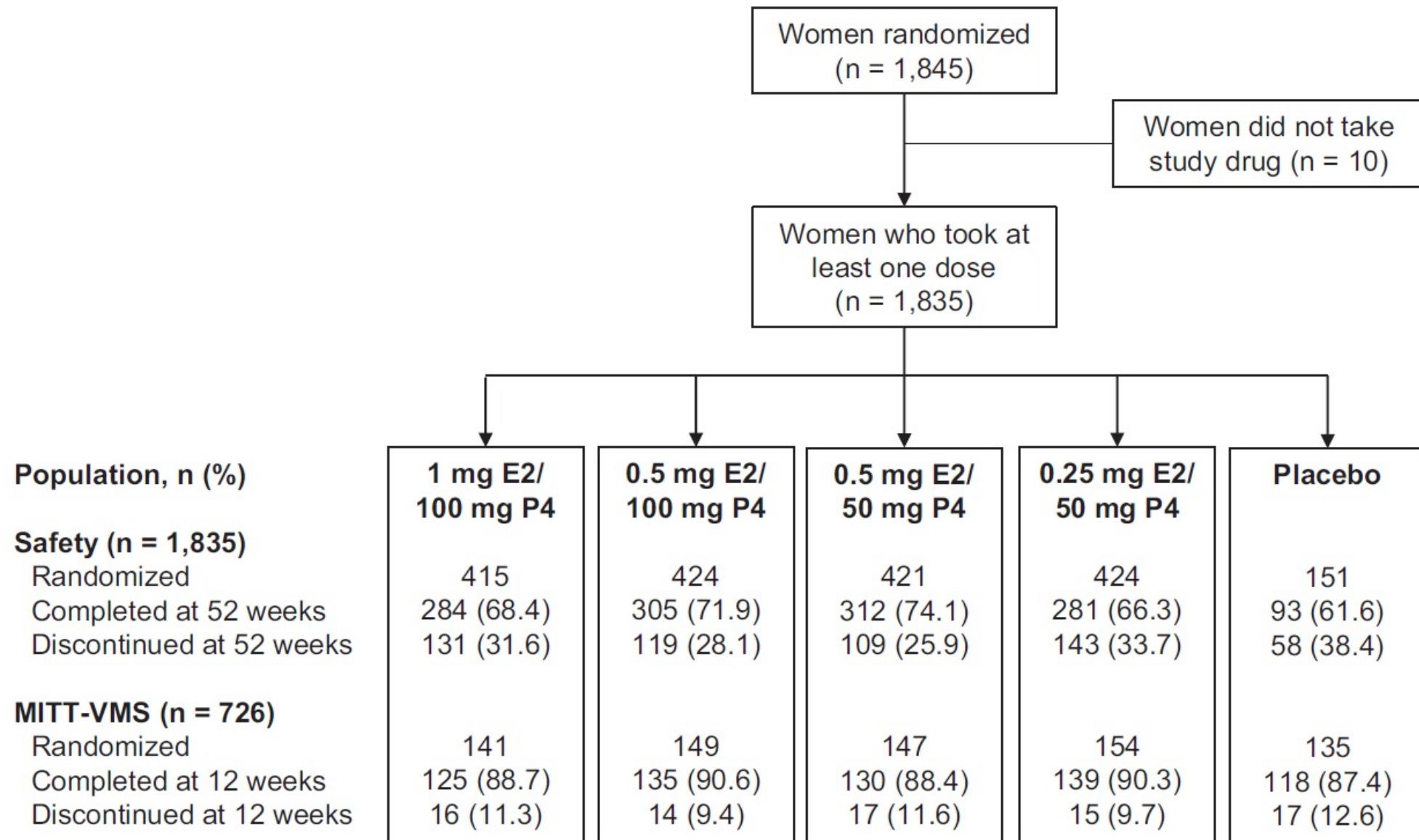
Safety: Endometrial hyperplasia incidence at 12 months in all women

Efficacy: Frequency and severity changes in moderate-to-severe vasomotor symptoms at weeks 4 and 12 in **VMS** sub-study

1. Lobo RA et al. Obstet Gynecol 2018; 132(1): 161-70.

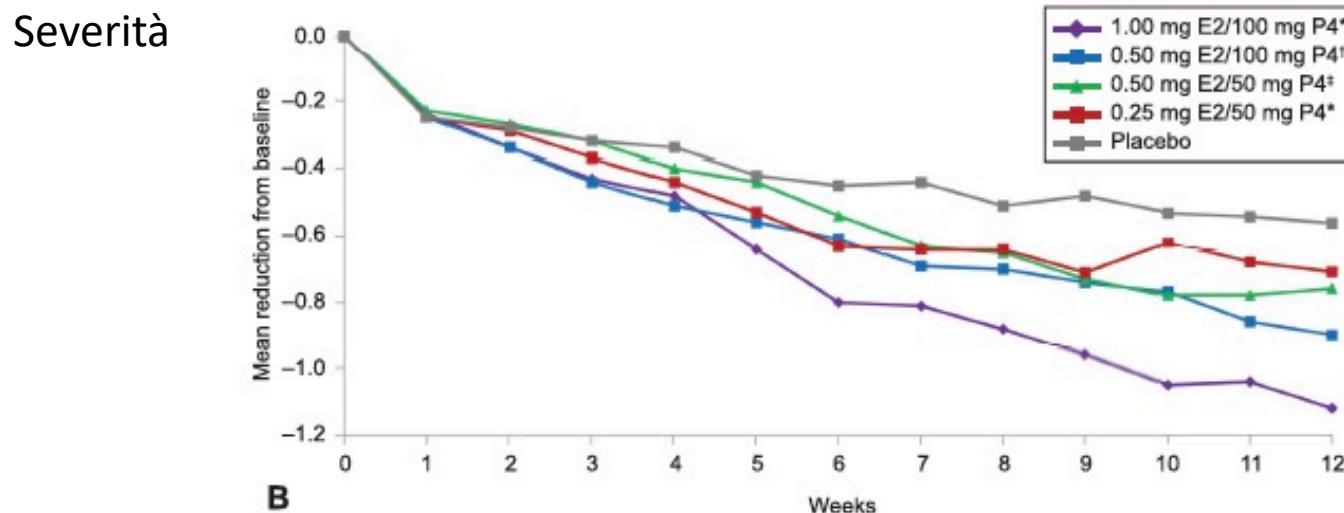
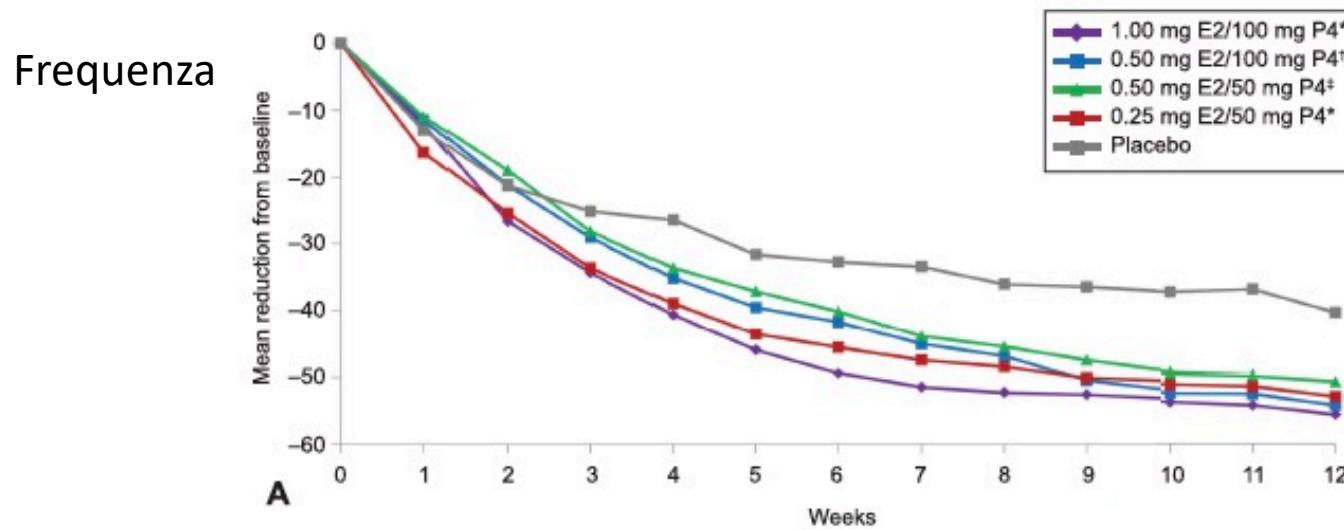
2. Archer DF et al. Expert Rev Clin Pharmacol. 2019; 12(8): 729-39.

3. Lobo RA et al. Menopause 2019; 26(7): 720-7.



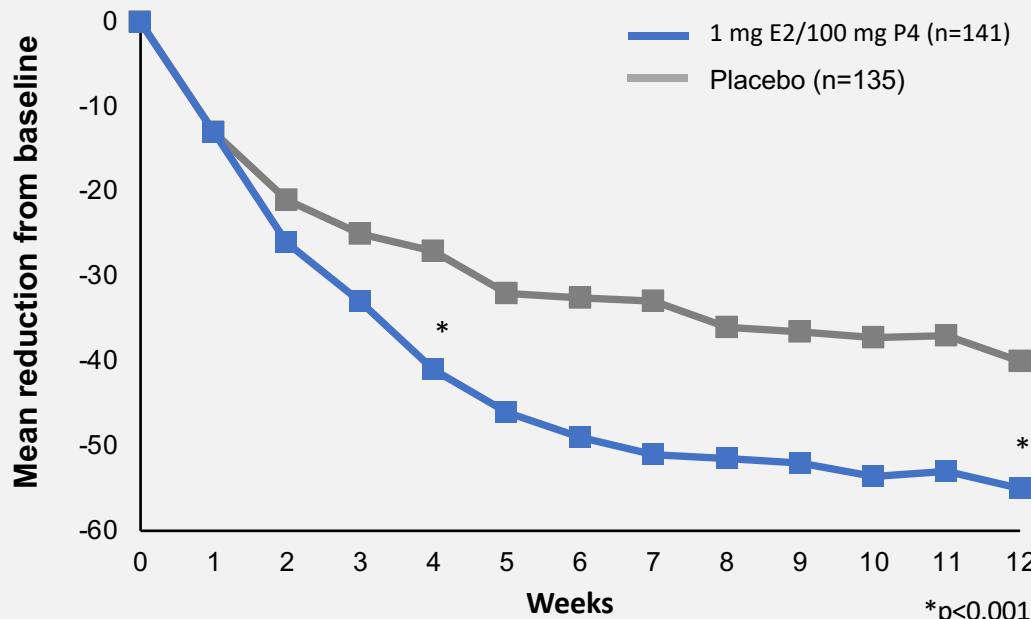
A 17 β -Estradiol–Progesterone Oral Capsule for Vasomotor Symptoms in Postmenopausal Women

A Randomized Controlled Trial

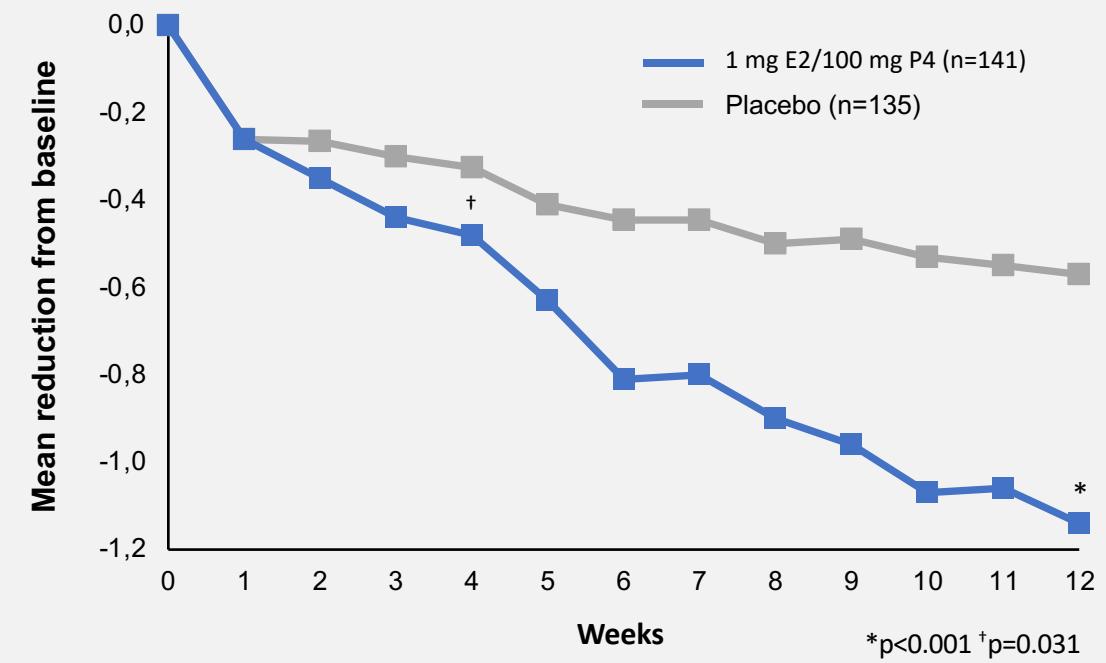


**REPLENISH co-primary endpoints:
Statistically significant reductions in frequency and severity of vasomotor symptoms^{1,2}**

Mean reduction in FREQUENCY of weekly moderate-to-severe vasomotor symptoms from week 1 through week 12



Mean reduction in SEVERITY of weekly moderate-to-severe vasomotor symptoms from week 1 through week 12



1. Theramex, Data on file.
2. Lobo RA et al. Obstet Gynecol 2018; 132(1): 161-70.

Evaluation of clinical meaningfulness of estrogen plus progesterone oral capsule (TX-001HR) on moderate to severe vasomotor symptoms

Ginger D. Constantine, MD,¹ Dennis A. Revicki, MD,² Risa Kagan, MD,³ James A. Simon, MD,⁴
Shelli Graham, PhD,⁵ Brian Bernick, MD,⁵ and Sebastian Mirkin, MD⁵

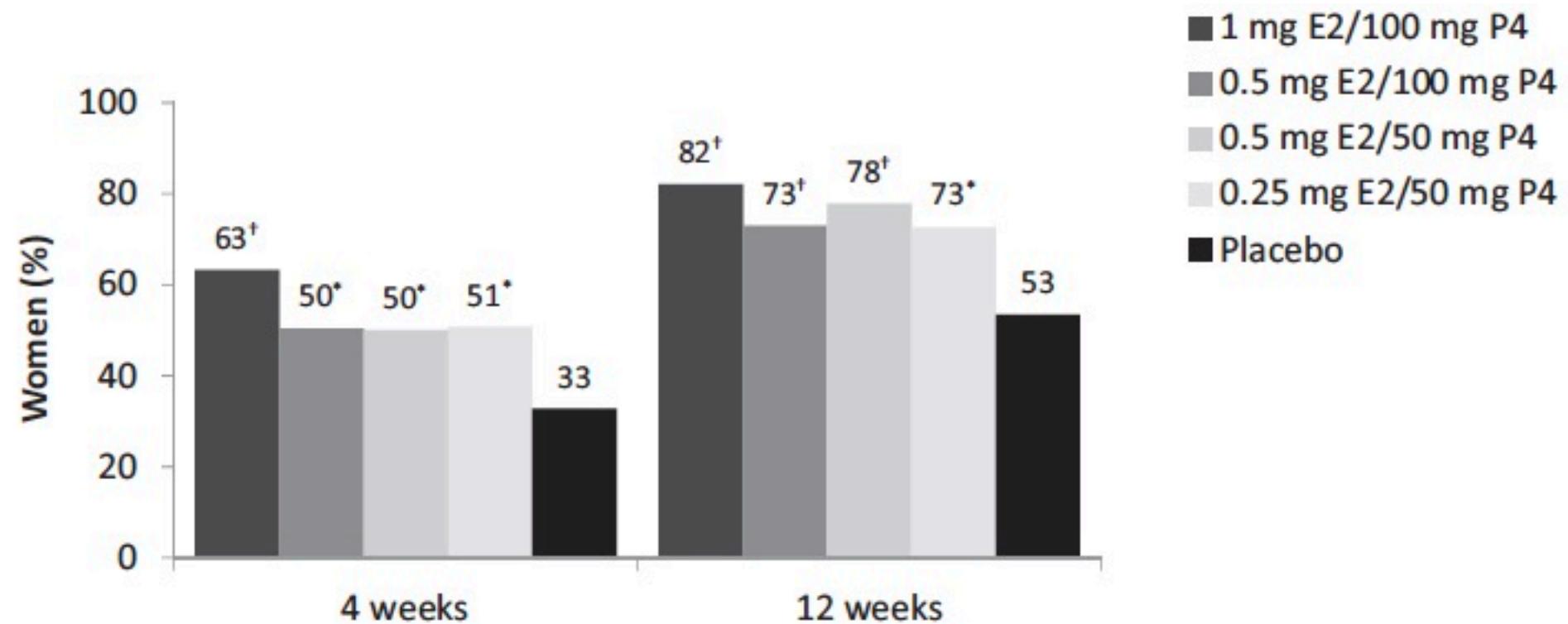
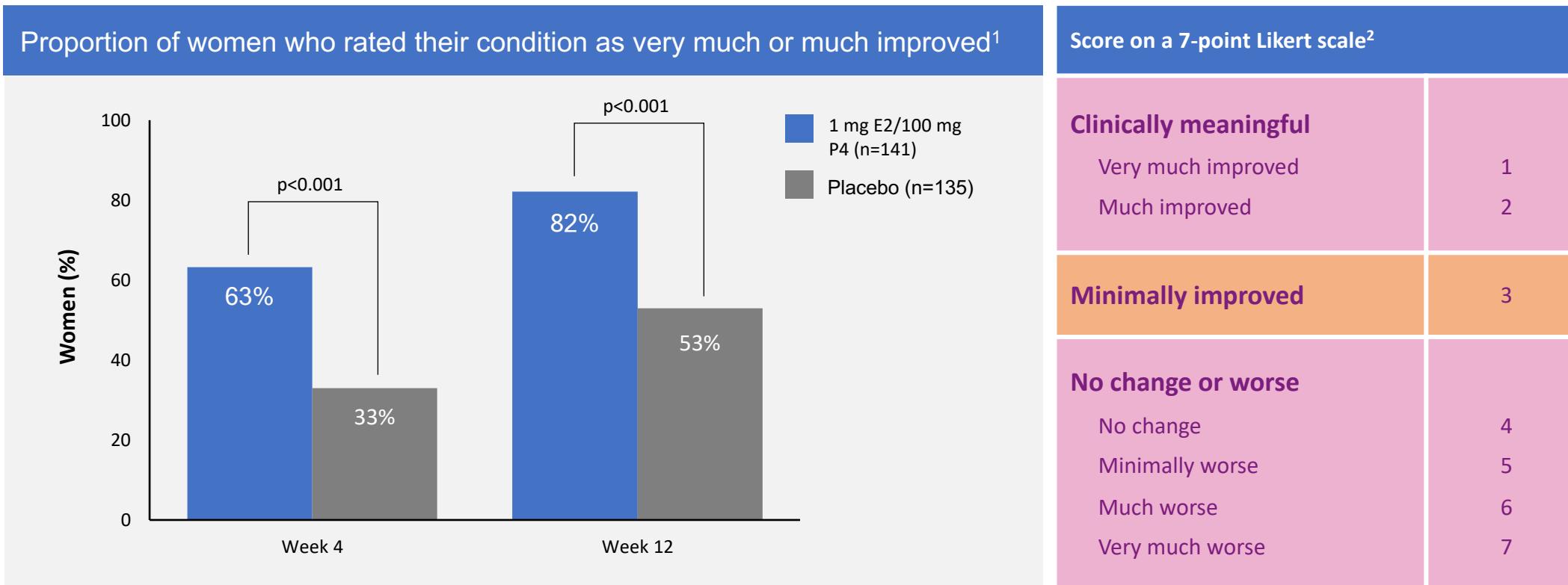


FIG. 1. Proportion of women who rated their condition as very much or much improved (Clinical Global Impression [CGI] response rate) at weeks 4 and 12. * $P < 0.01$; [†] $P < 0.001$ versus placebo, calculated with Fisher exact test.

REPLENISH CGI response: Significantly more women with a clinically meaningful improvement vs placebo¹

Women in the VMS sub study answered the following question:

“Rate the total improvement, whether or not in your judgment it is due entirely to drug treatment. Compared to your condition at admission to the study, how much has it changed?”



1. Constantine GD et al. Menopause 2019; 26(5): 513-9.
2. Spearing MK et al. Psychiatry Res 1997; 73(3): 159-71.

CGI: clinical Global Impression; VMS: vasomotor symptom

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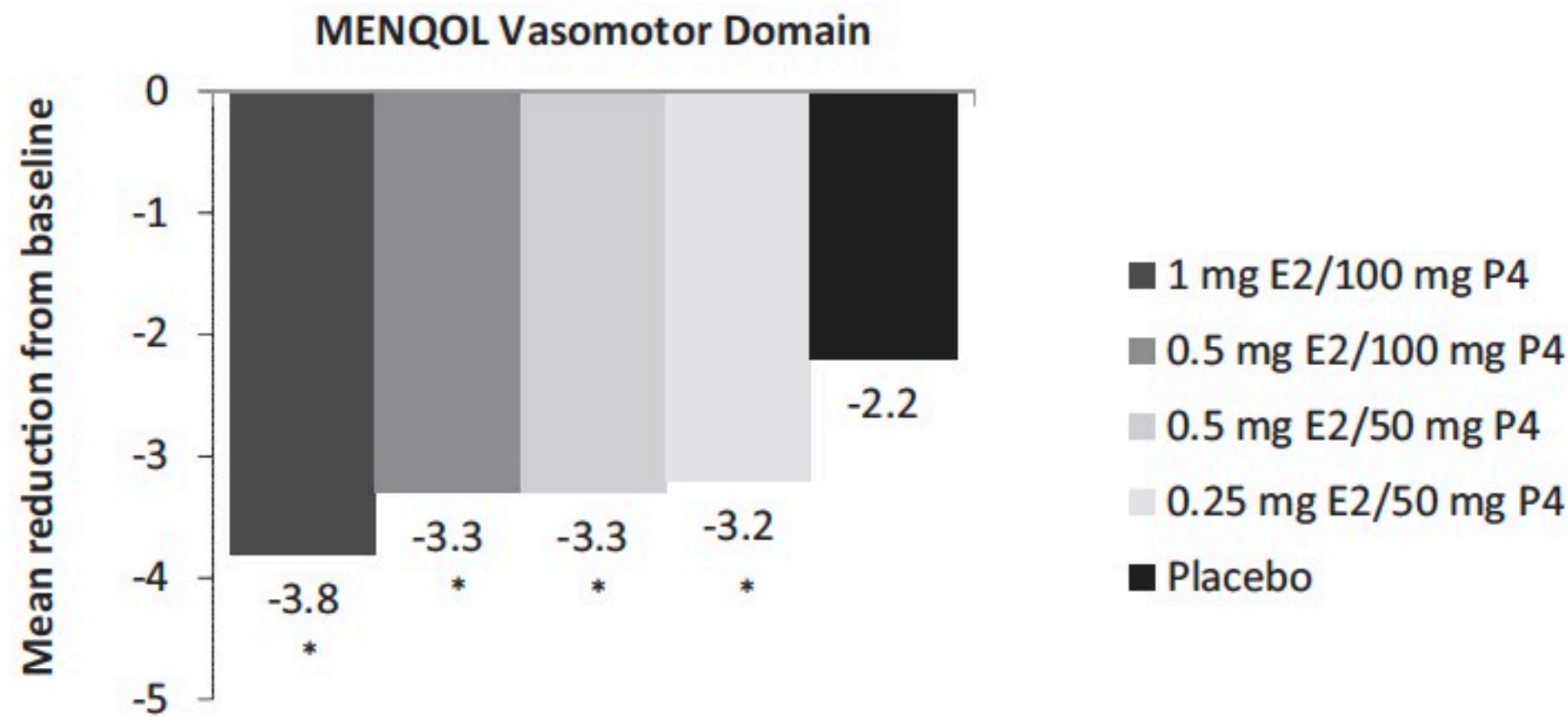
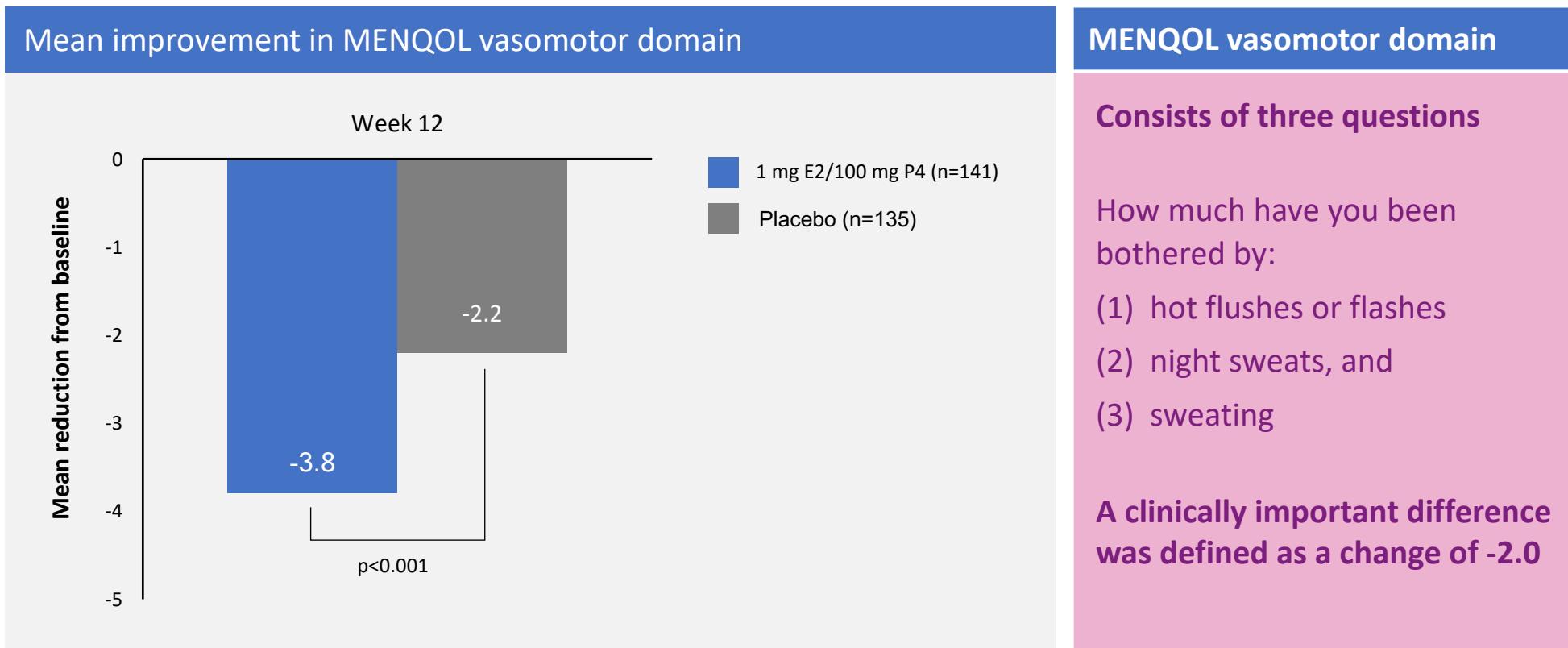


FIG. 3. Change from baseline in Menopause-Specific Quality of Life questionnaire (MENQOL) vasomotor domain at week 12. * $P < 0.001$ versus placebo in least squares mean, derived from the analysis of covariance (ANCOVA) model with treatment as factors and baseline as covariate.

REPLENISH MENQOL response: Significantly greater improvements in menopause-specific quality of life vs placebo¹

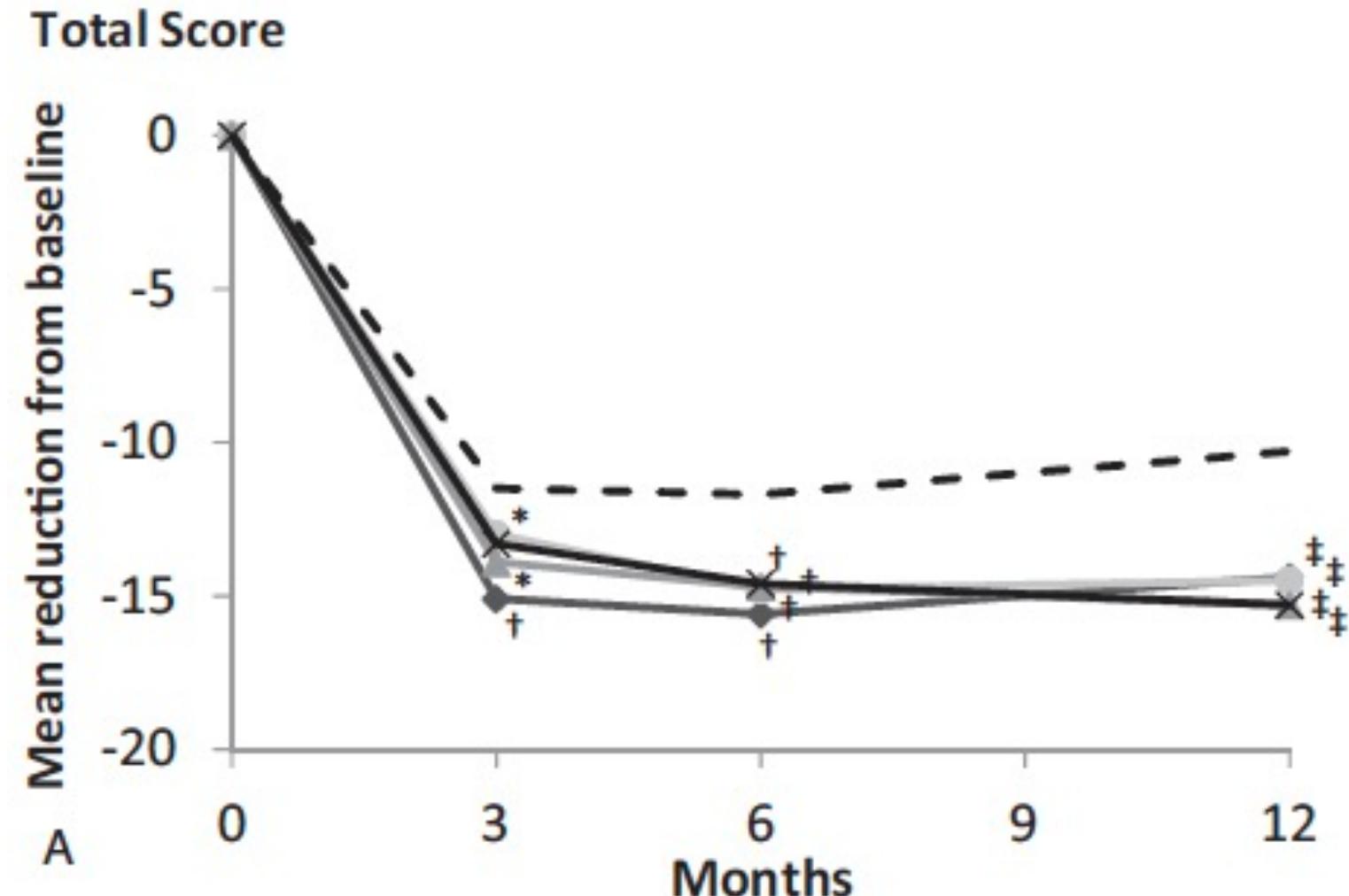
The self-administered MENQOL assesses the impact of menopausal symptoms as experienced over the last month



1. Constantine GD et al. Menopause 2019; 26(5): 513-9.

Improvement in sleep outcomes with a 17 β -estradiol–progesterone oral capsule (TX-001HR) for postmenopausal women

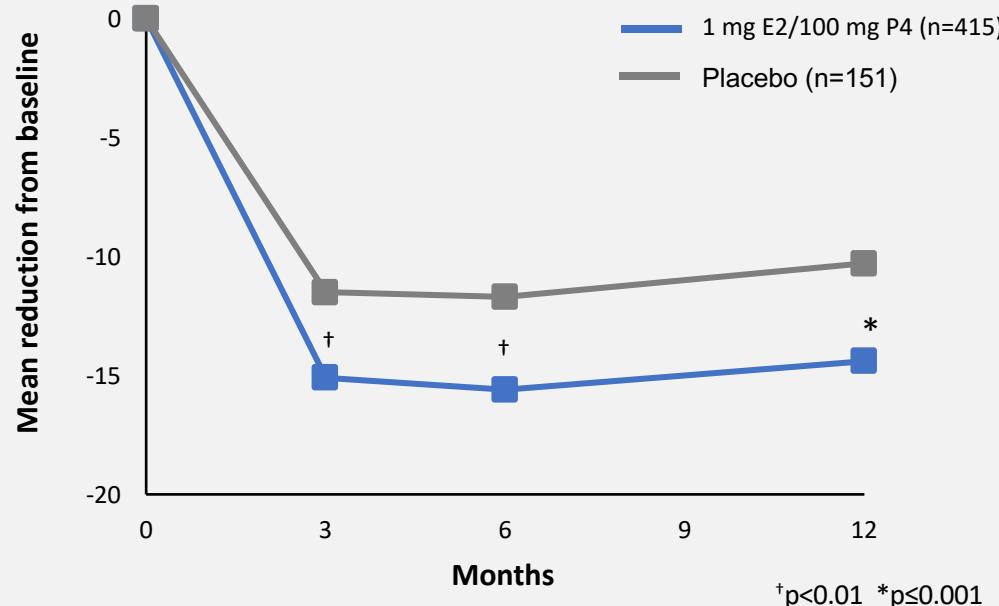
Risa Kagan, MD, FACOG, CCD, NCMP,¹ Ginger Constantine, MD,²
Andrew M. Kaunitz, MD,³ Brian Bernick, MD,⁴ and Sebastian Mirkin, MD⁴



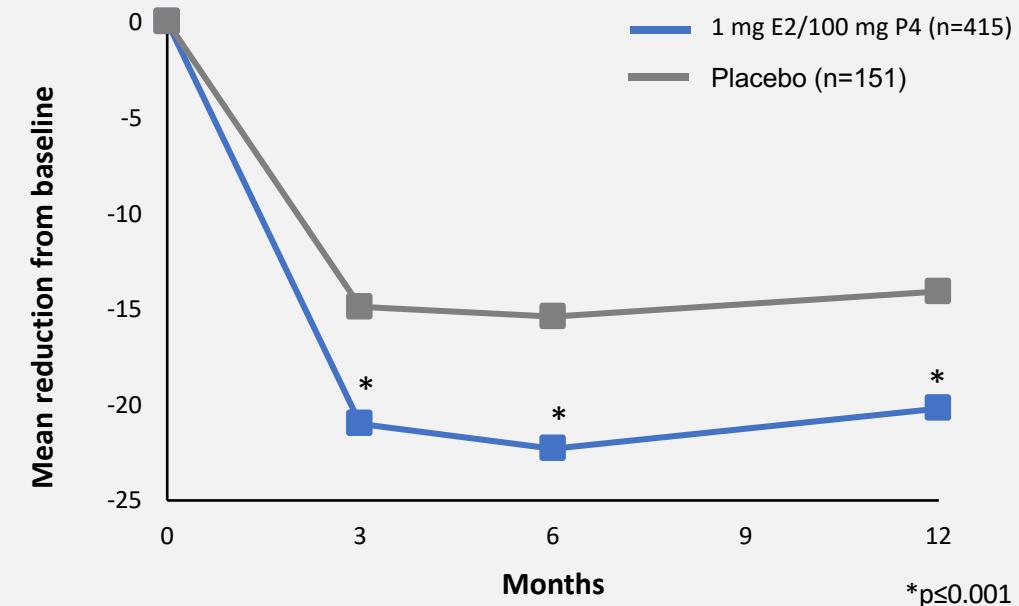
REPLENISH MOS-Sleep outcomes: Statistically significantly and sustainably improved sleep parameters vs placebo¹

The self-reported MOS-Sleep scale addresses time to fall asleep, hours of sleep, sleep maintenance, respiratory problems, perceived sleep adequacy, and somnolence over the past 4 weeks

Mean improvement in MOS-Sleep total score over 12 months



Mean improvement in MOS-Sleep disturbance score over 12 months



1. Kagan R et al. Menopause 2019; 26(6): 622-8.

Endometrial safety and bleeding profile of a 17 β -estradiol/progesterone oral softgel capsule (TX-001HR)*

Sebastian Mirkin, MD,¹ Steven R. Goldstein, MD,² David F. Archer, MD,³ James H. Pickar, MD,⁴
Shelli Graham, PhD,¹ and Brian Bernick, MD¹

TABLE 2. *Endometrial safety endpoints in endometrial safety population*

Treatment, n (%)	Estradiol/progesterone				Placebo (n = 92)
	1 mg/100 mg (n = 281)	0.5 mg/100 mg (n = 303)	0.5 mg/50 mg (n = 306)	0.25 mg/50 mg (n = 274)	
Hyperplasia at 12 mos^a					
Incidence rate	1 (0.36)	0	0	0	0
One-sided upper 95% CI	1.97%	0.98%	0.97%	1.09%	3.93%
Proliferative endometrium^b					
Screening	2 (0.7)	5 (1.7)	2 (0.7)	1 (0.4)	0
Month 12	8 (2.9)	5 (1.7)	1 (0.3)	3 (1.1)	0
Weakly proliferative					
Screening	0	0	0	0	0
Month 12	1 (0.4)	2 (0.7)	2 (0.7)	2 (0.7)	0
Endometrial polyps					
Screening	5 (1.8)	7 (2.3)	5 (1.6)	5 (1.8)	0
Month 12	4 (1.4)	6 (2.0)	10 (3.3)	7 (2.6)	0

CI, confidence interval.

^aAn incidence rate of $\leq 1\%$ with an upper limit of the one-sided 95% CI being $\leq 4\%$ was considered acceptably low.²

^bIncludes proliferative and disordered proliferative endometrium.

**REPLENISH primary safety endpoint:
Endometrial hyperplasia incidence <1% at 12 months¹**

Endometrial biopsy assessments revealed **one case of endometrial hyperplasia** and no cases of endometrial cancer in women who received 1 mg E2/100 mg P4¹

Endometrial Hyperplasia incidence rate (%)	
1 mg E2/100 mg P4 n=281	Placebo n=92
1 (0.36%)	0 (0.00%)

US Food and Drug Administration guidance recommend that the incidence of endometrial hyperplasia in HRT trials should be less than 1% at 12 months, and similar to an untreated population²

- therefore endometrial protection as defined by the FDA was accomplished with the P4 component of treatment¹

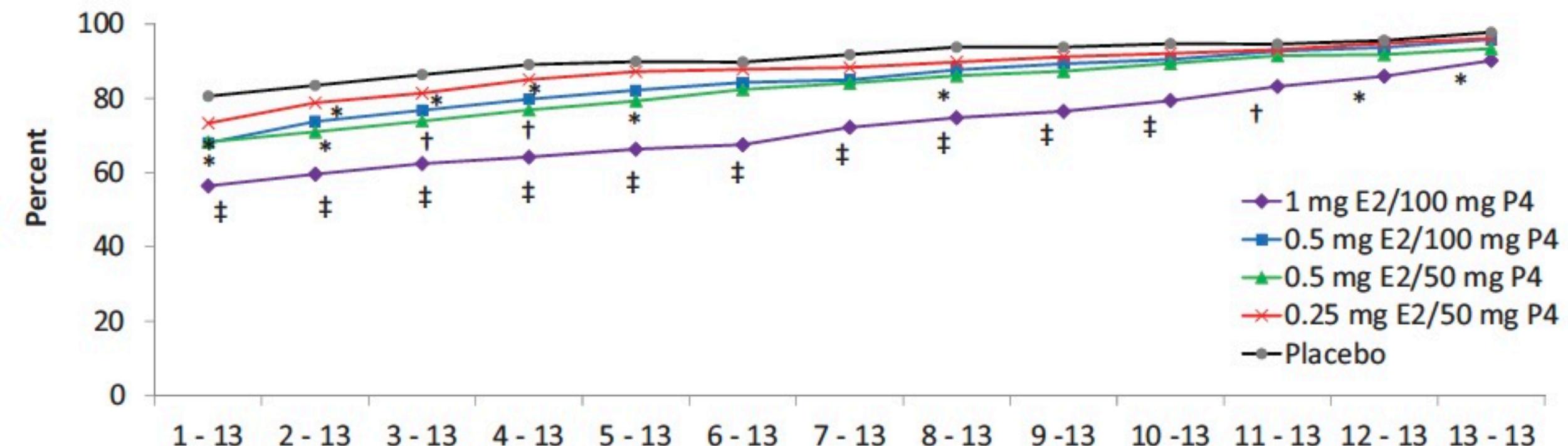
1. Mirkin S et al. Menopause 2020; 27(4): 410-17.

2. FDA Guidance for Industry. Available at: <https://www.fda.gov/media/75802/download> Accessed on: 20.01.21.

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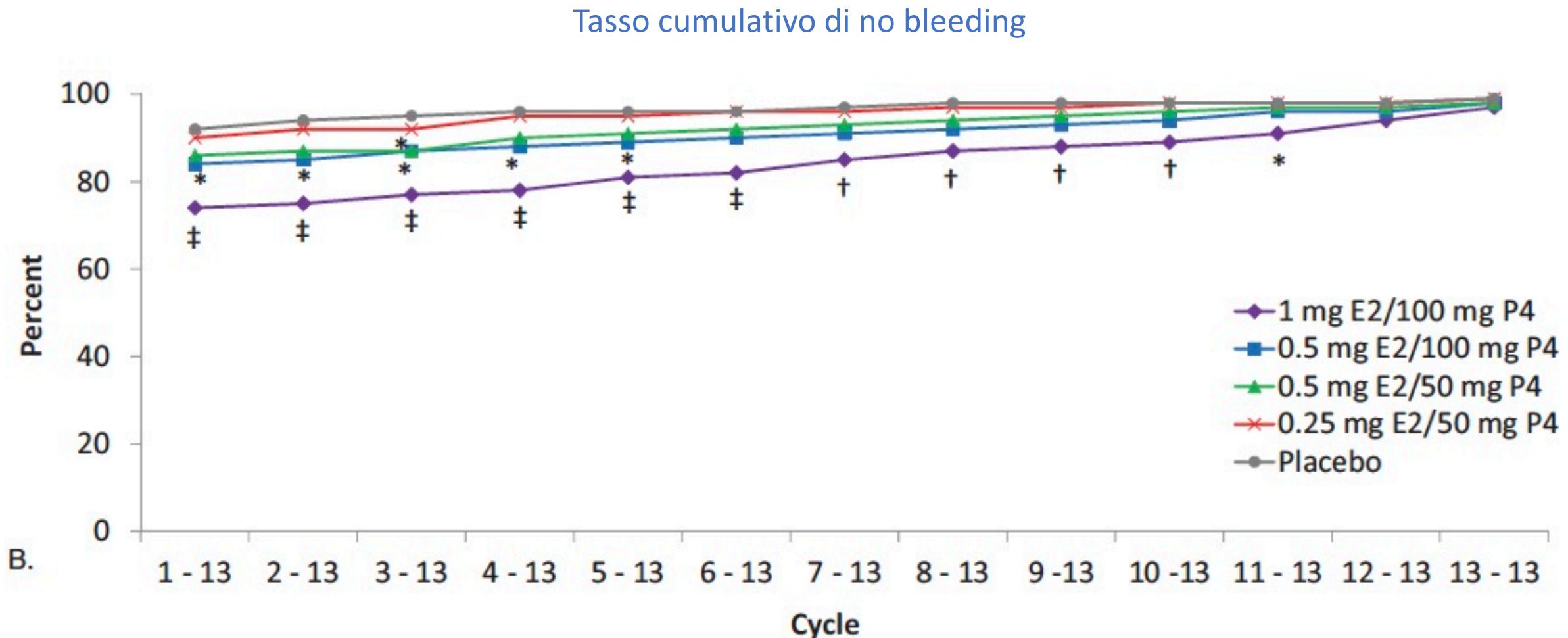
Tasso cumulativo di amenorrea (no bleeding – no spotting)



Nel gruppo 1mgE2/100mgP4 il tasso cumulativo di amenorrea a 13 mesi è pari al 90.2%
Nel corso dello studio il 56.1% dei soggetti presenta amenorrea

Endometrial safety and bleeding profile of a 17β -estradiol/progesterone oral softgel capsule (TX-001HR)*

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Nel gruppo 1mgE2/100mgP4 il tasso cumulativo di no bleeding a 13 mesi è pari al 97%
Nel corso dello studio il 73.4% dei soggetti presenta no bleeding

REPLENISH:

Cumulative amenorrhea and no bleeding rates

Consecutive cycles of no bleeding or spotting

From cycles 1 to 13

1 mg E2/100 mg P4: **56.1%**

Placebo: **78.9%**

p<0.001

In cycle 13

1 mg E2/100 mg P4: **90.2%**

Placebo: **97.8%**

Consecutive cycles of no bleeding

From cycles 1 to 13

1 mg E2/100 mg P4: **73.4%**

Placebo: **91.1%**

p<0.001

In cycle 13

Both 1 mg E2/100 mg P4
and placebo: **>97%**

TABLE 4. *Cumulative amenorrhea rates with menopausal hormone therapies^a*

Products	Doses	Cumulative amenorrhea (%) cycle 1 to cycle 13
Oral		
Prempro (CEE/MPA; Wyeth Pharmaceuticals Inc, Philadelphia, PA) ¹⁷	0.625 mg/5 mg 0.625 mg/2.5 mg 0.45 mg/1.5 mg 0.3 mg/1.5 mg	26 23 42 45
Activella (E2/NETA; Novo Nordisk Inc, Princeton, NJ) ¹⁸	1 mg/0.5 mg	49
Angeliq (E2/DRSP; Bayer Healthcare, Whippany, NJ) ¹⁹	1 mg/0.5 mg	45
TX-001HR (E2/P4)	1 mg/100 mg	56
Placebo (REPLENISH trial)		81
Transdermal patch		
CombiPatch (E2/NETA; Novartis Pharmaceuticals, East Hanover, NJ) ²⁰	0.05 mg/0.14 mg 0.05 mg/0.25 mg	27 9
Climara Pro (E2/LNG; Berlex, Montville, NJ) ²¹	0.045 mg/ 0.015 mg	16

CEE, conjugated equine estrogens; DRSP, drospirenone; E2, 17 β -estradiol; EE, ethinyl estradiol; LNG, levonorgestrel; MPA, medroxyprogesterone acetate; NETA, norethisterone acetate; P4, progesterone.

^aBased on prescribing information or clinical data; not a head-to-head comparison.

REPLENISH adverse events:
Treatment-emergent AEs in both groups largely mild to moderate¹

Treatment-related TEAEs occurring $\geq 3\%$ of the 1 mg E2/100 mg P4 group		
	1 mg E2/100 mg P4 (n=415)	Placebo (n=151)
Any treatment-related TEAE	170 (41%)	27 (18%)
Breast tenderness	43 (10%)	1 (1%)
Headache	14 (3%)	1 (1%)
Vaginal haemorrhage	14 (3%)	0 (0%)
Vaginal discharge	14 (3%)	1 (1%)
Pelvic pain	13 (3%)	0 (0%)
Nausea	9 (2%)	1 (1%)
Any treatment-related SAE	3 (0.7%)	1 (0.7%)

1. Archer DF *et al*. Expert Rev Clin Pharmacol 2019; 12(8): 729-39.

SAE: serious adverse events

TEAE: treatment emergent adverse event

Breast effects of oral, combined 17 β -estradiol, and progesterone capsules in menopausal women: a randomized controlled trial

James H. Liu, MD,¹ Denise R. Black, MD,² Lisa Larkin, MD,³ Shelli Graham, PhD,⁴ Brian Bernick, MD,⁴ and Sebastian Mirkin, MD⁴

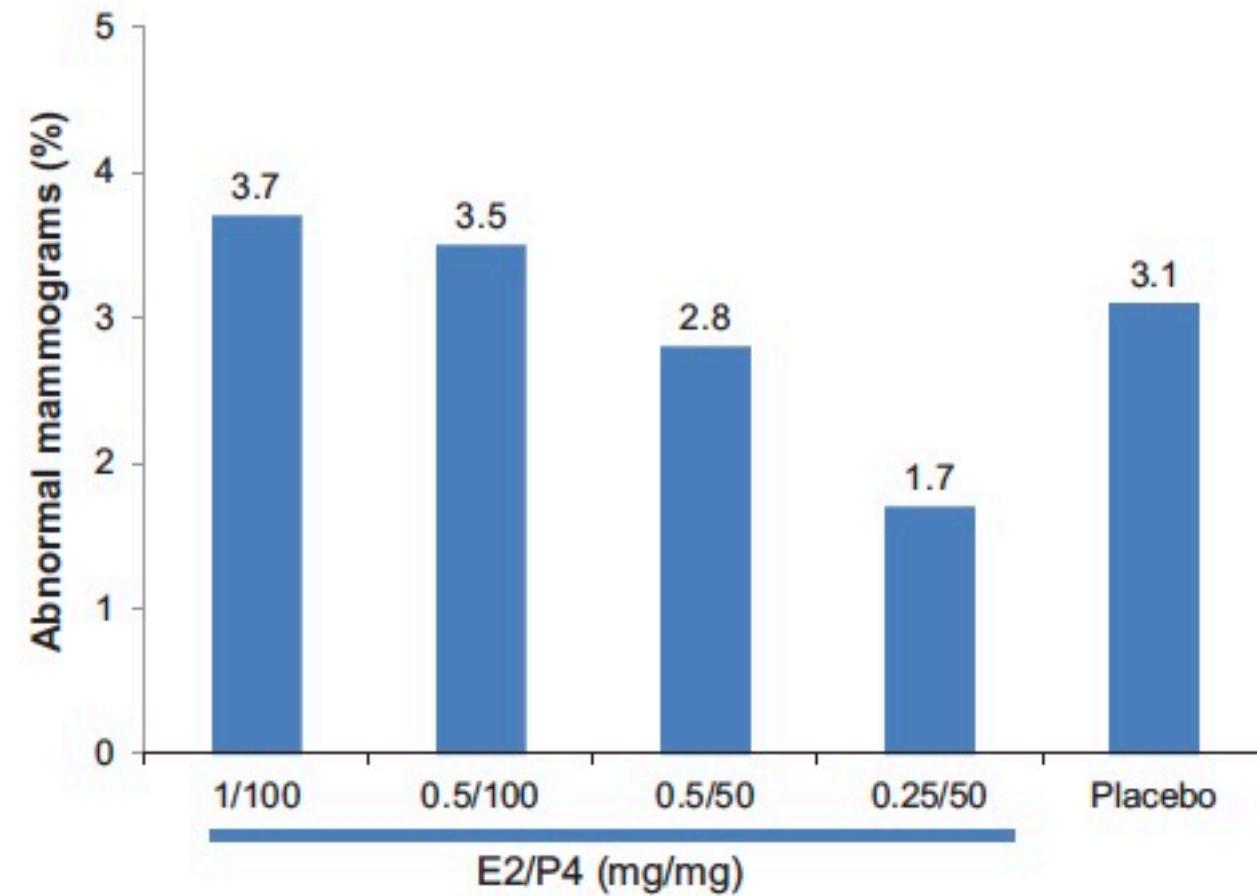


FIG. 2. Incidence of abnormal mammograms at study end. E2, 17 β -estradiol; P4, progesterone.

Abnormal mammogram rates consistent with background incidence¹

- In the 1-year 1 mg estradiol/100 mg progesterone trial, incidence of **abnormal mammograms** was consistent with that of women taking placebo (3.1% vs. 3.7%)¹
 - The incidence of abnormal screening mammograms in the US is 5%-6%²
 - At the end of the first year of the WHI study, the incidence of abnormal mammograms was 9.4% in women taking Prempro® vs. 5.4% for placebo (but mean age was higher)³

1. Archer DF Endocrine Reviews, Volume 39, Issue 2 Supplement, April 2018. 2. Monticciolo DL et al. Breast J. 2004;10:106-110. .

2. Liu JH Menopause 2020 Volume 27 pp. 1381-1395

3. Chlebowski RT, et al. JAMA. 2003;289:3243-3253

TABLE 4. Incidence of breast-related adverse events of interest

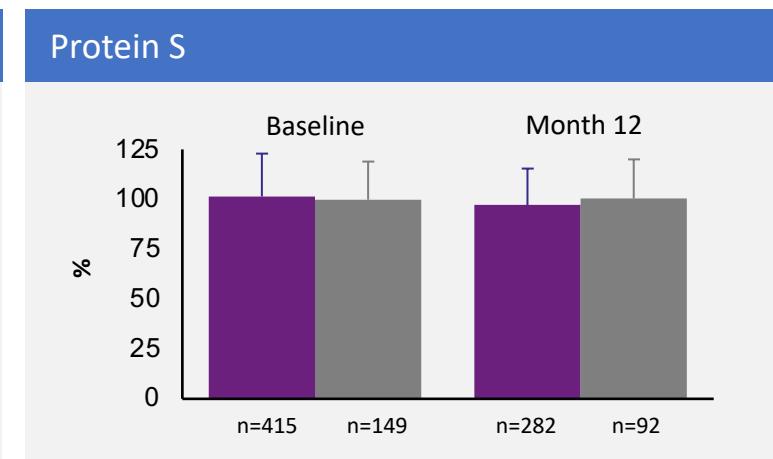
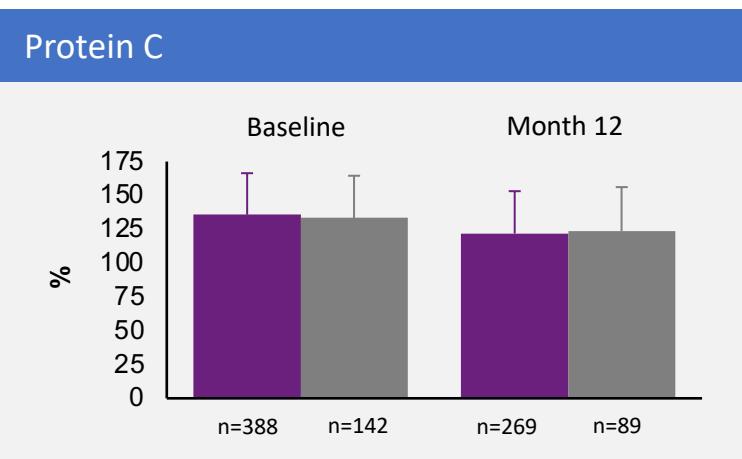
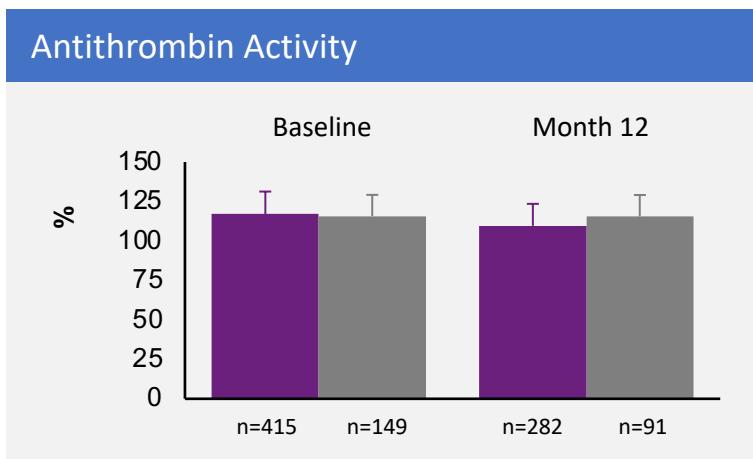
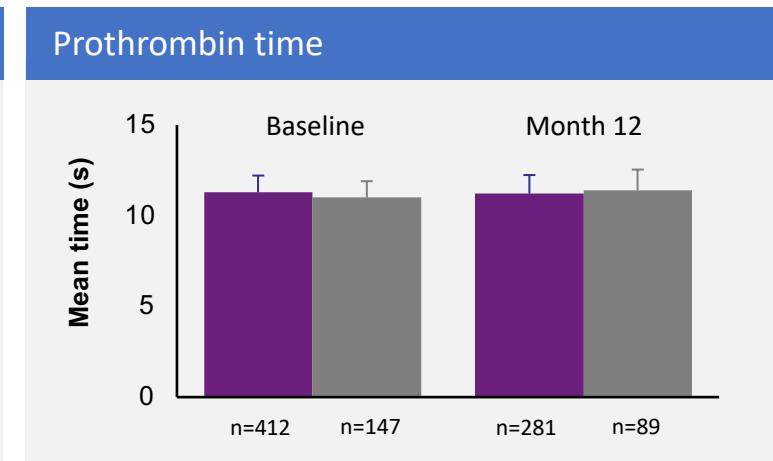
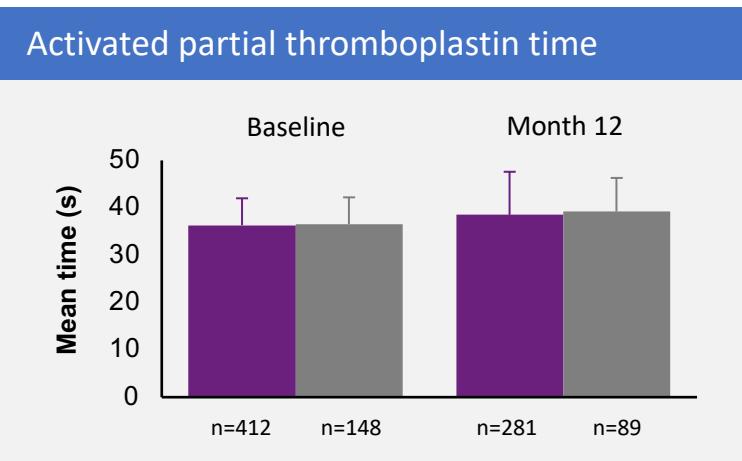
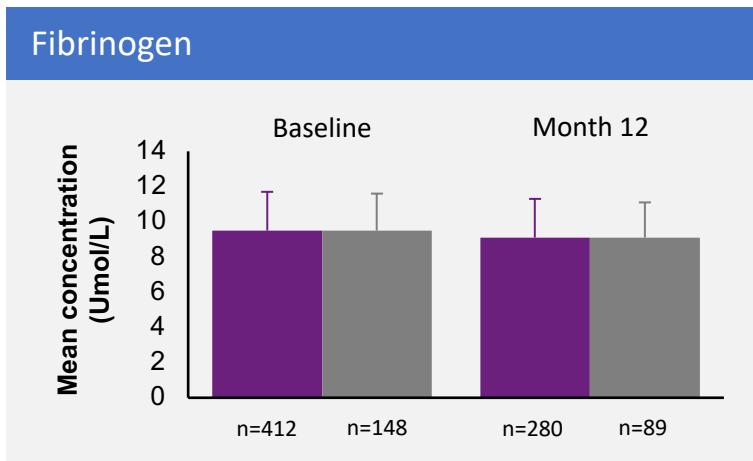
	1 mg E2/100 mg P4 (n=415)	0.5 mg E2/100 mg P4 (n=424)	0.5 mg E2/50 mg P4 (n=421)	0.25 mg E2/50 mg P4 (n=424)	Placebo (n=151)
AEs, n (%)					
Breast cancer ^a	2 (0.5)	2 (0.5)	1 (0.2)	1 (0.2)	0 (0.0)
[95% CI]	[0.1-1.7]	[0.1-1.7]	[0.0-1.3]	[0.0-1.3]	[0.0-2.4]
P value ^b	>0.9999	>0.9999	>0.9999	>0.9999	
Benign breast neoplasm	4 (1.0)	5 (1.2)	4 (1.0)	3 (0.7)	1 (0.7)
[95% CI]	[0.3-2.4]	[0.4-2.7]	[0.3-2.4]	[0.1-2.1]	[0.0-3.6]
P-value ^b	>0.9999	>0.9999	>0.9999	>0.9999	
Breast calcifications	3 (0.7)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
[95% CI]	[0.1-2.1]	[0.0-0.9]	[0.0-0.9]	[0.0-1.3]	[0.0-2.4]
P value ^b	0.5685			>0.9999	
Breast cyst	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
[95% CI]	[0.0-1.3]	[0.0-0.9]	[0.0-0.9]	[0.0-0.9]	[0.0-2.4]
P value ^b	>0.9999				
Breast mass	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
[95% CI]	[0.0-0.9]	[0.0-1.3]	[0.0-0.9]	[0.0-0.9]	[0.0-2.4]
P value ^b		>0.9999			
TEAEs, n (%)					
Breast tenderness	45 (10.8)	19 (4.5)	25 (5.9)	10 (2.4)	1 (0.7)
[95% CI]	[8.0-14.2]	[2.7-6.9]	[3.9-8.6]	[1.1-4.3]	[0.0-3.6]
P-value ^b	<0.0001	0.0348	0.0052	0.3035	
Breast pain	9 (2.2)	2 (0.5)	1 (0.2)	2 (0.5)	0 (0.0)
[95% CI]	[1.0-4.1]	[0.1-1.7]	[0.0-1.3]	[0.1-1.7]	[0.0-2.4]
P-value ^b	0.1215	>0.9999	>0.9999	>0.9999	
Breast discomfort	3 (0.7)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
[95% CI]	[0.1-2.1]	[0.0-1.3]	[0.0-0.9]	[0.0-0.9]	[0.0-2.4]
P value ^b	0.5685	>0.9999			
Breast swelling	2 (0.5)	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)
[95% CI]	[0.1-1.7]	[0.0-0.9]	[0.1-1.7]	[0.0-0.9]	[0.0-2.4]
P value ^b	>0.9999		>0.9999		

AE, adverse event; TEAE, treatment-emergent adverse event; E2, 17 β -estradiol; P4, progesterone.^aBreast cancer includes invasive ductal breast carcinoma.^bP value was calculated for active dose versus placebo.

TABLE 6. Risk of breast cancer with hormone therapy containing progesterone or progestins in large observational studies

Study	Estrogen and/or progestogen	HR (95% CI)
Fournier et al, 2014 ⁶	Estrogen alone	1.17 (0.99-1.38)
	Estrogen plus progesterone/dydrogesterone	1.22 (1.11-1.35)
	Estrogen plus synthetic progestins	1.87 (1.71-2.04)
Cordina-Duverger et al, 2013 ⁷	Estrogen alone (any)	1.19 (0.69-2.04)
	Estrogen (any) with progestogens	1.33 (0.92-1.92)
	Natural progesterone	0.80 (0.44-1.43)
	Synthetic progestins	1.72 (1.11-2.65)
	Progesterone derivatives	1.57 (0.99-2.49)
	Testosterone derivatives	3.35 (1.07-10.4)
Fournier et al, 2008 ⁵	Oral estrogen alone	1.32 (0.76-2.29)
	Oral estrogen plus progestogen	
	Progesterone	Not analyzed ^a
	Dydrogesterone	0.77 (0.36-1.62)
	Medrogestone	2.74 (1.42-5.29)
	Chlormadinone acetate	2.02 (1.00-4.06)
	Cyproterone acetate	2.57 (1.81-3.65)
	Promegestone	1.62 (0.94-2.82)
	Nomegestrol acetate	1.10 (0.55-2.21)
	Norethisterone acetate	2.11 (1.56-2.86)
	Medroxyprogesterone acetate	1.48 (1.02-2.16)
	Transdermal estrogen alone	1.28 (0.98-1.69)
	Transdermal estrogen plus progestogen	
	Progesterone	1.08 (0.89-1.31)
	Dydrogesterone	1.18 (0.95-1.48)
	Medrogestone	2.03 (1.39-2.97)
	Chlormadinone acetate	1.48 (1.05-2.09)
	Cyproterone acetate	Not analyzed ^a
	Promegestone	1.52 (1.19-1.96)
	Nomegestrol acetate	1.60 (1.28-2.01)
	Norethisterone acetate	Not analyzed ^a
	Medroxyprogesterone acetate	Not analyzed ^a
Fournier et al, 2005 ⁴	Estrogen alone	1.1 (0.8-1.6)
	Estrogen plus progesterone	0.9 (0.7-1.2)
	Transdermal estrogen	0.9 (0.7-1.2)
	Oral estrogen	No events
	Estrogen plus synthetic progestins	1.4 (1.2-1.7)
	Transdermal estrogen	1.4 (1.2-1.7)
	Oral estrogen	1.5 (1.1-1.9)

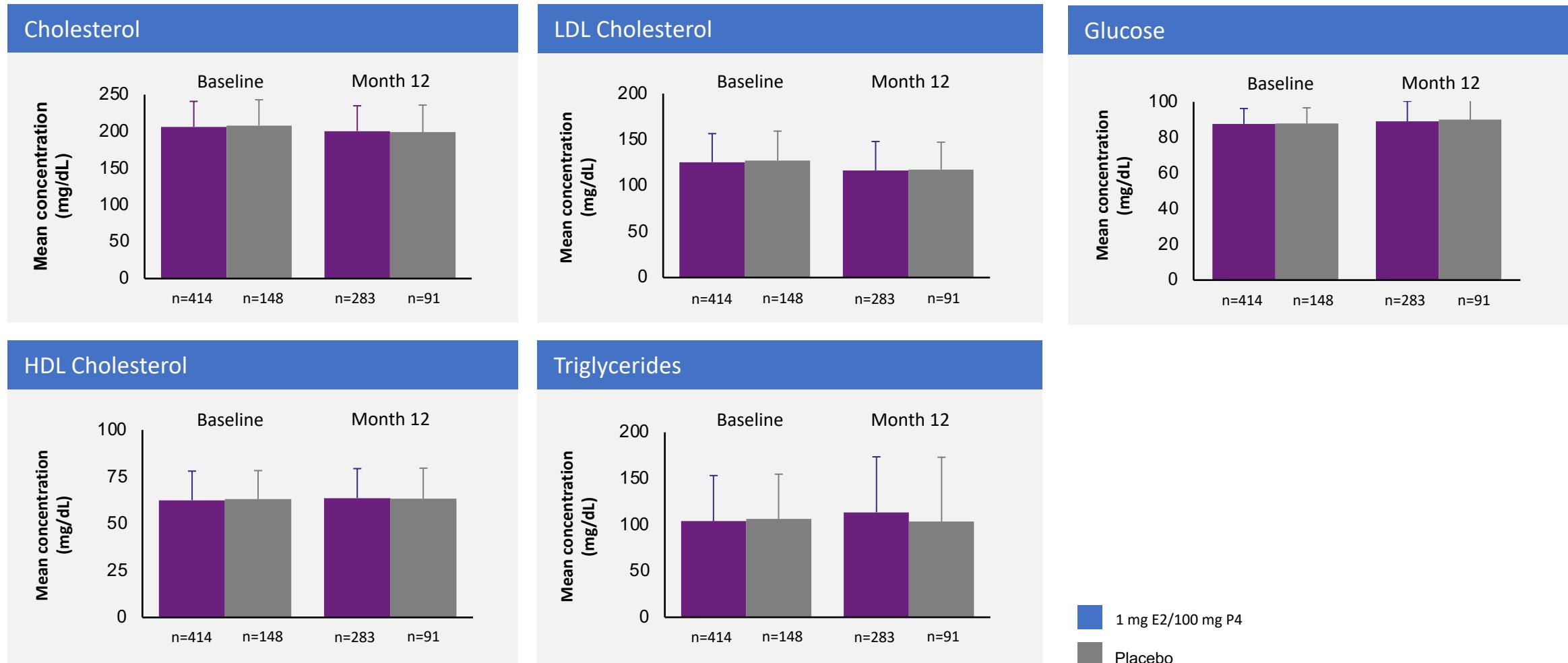
- REPLENISH:
- No clinically meaningful changes in coagulation parameters observed¹



1 mg E2/100 mg P4 Placebo

1. Lobo RA et al. Climacteric 2019; 22(6): 610-16.

- REPLENISH:
- No clinically meaningful changes in lipid or glucose parameters observed¹

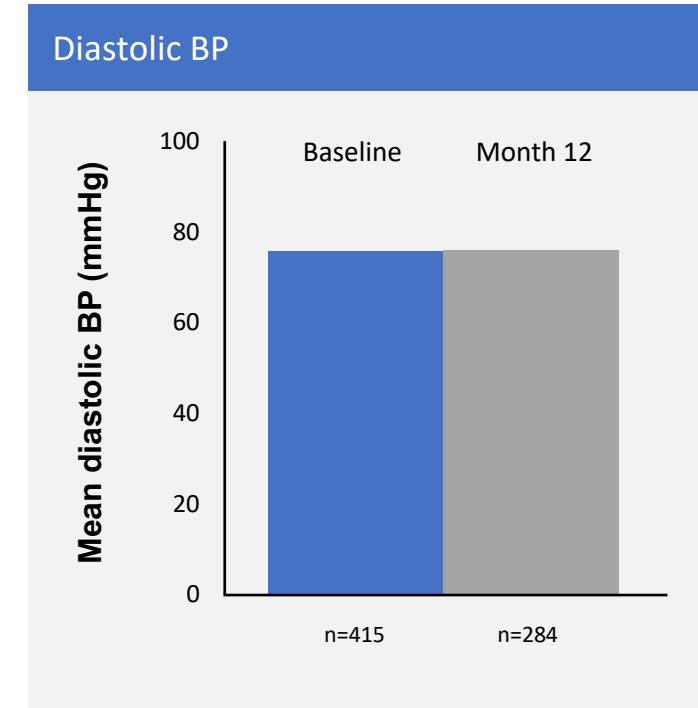
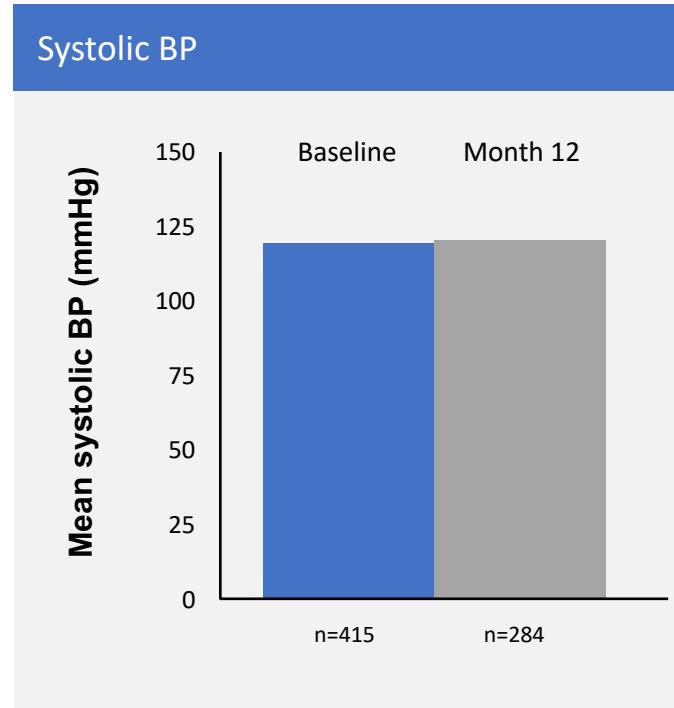
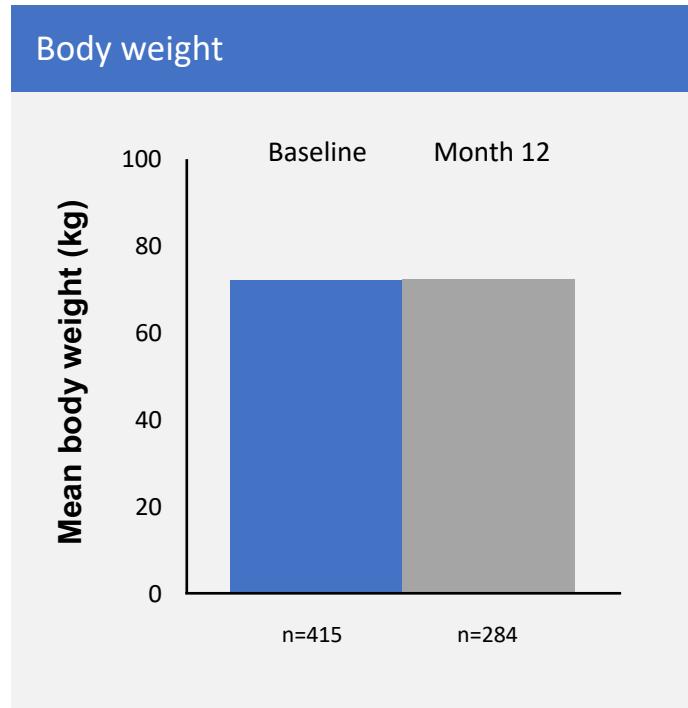


1. Lobo RA et al. Climacteric 2019; 22(6): 610-16.

LDL: low-density lipoprotein

HDL: high-density lipoprotein

- REPLENISH:
- No clinically meaningful changes in body weight, systolic or diastolic blood pressure observed¹



■ 1 mg E2/100 mg P4 ■ Month 12

1. Black DR et al. Menopause 2020; 28(1): 32-9.

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Stable E2 serum levels to provide effective vasomotor symptom relief



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- Clinically meaningful benefits demonstrated with the CGI, MENQOL and MOS-Sleep analyses
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- No clinically meaningful impact on lipids, glucose, coagulation parameters, liver function tests, systolic or diastolic BP, or weight

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