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Alternative Hormonal Treatments

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Effects of selected ERAAs on target tissues in humans

ERAA	Endometrium	Vagina	Breast	Bone
Ospemifene	Partial agonist[43-46] • Up to 52-wk RCT • Slight ↑ in thickness from BL by TVU • Generally no histologic changes from BL • No reports of cancer	Agonist[43-46] • Up to 52-wk RCT • SS ↑ in superficial cells • SS ↓ in parabasal cells • SS ↓ in pH • $P < 0.001$ for all vs PBO	Neutral (limited data)[43-46] • Up to 52-wk RCT • No clinically significant abnormalities by mammography • No reports of cancer during these RCTs[a]	Agonist (limited data)[47,48] • 3-mo RCT • Positive effects of bone turnover on biomarkers
Tamoxifen	Agonist[49-51] • Meta-analysis of four trials • SS ↑ in cancer ($P < 0.001$) vs PBO • ↑ in thickness[b]	Agonist[52] • Prospective study • SS ↑ in MI across 24 mo vs controls ($P < 0.0001$)	Antagonist[51] • Meta-analysis of four trials • SS ↓ in cancer vs PBO ($P < 0.0001$)	Agonist[53] • 2-y RCT • SS ↑ in lumbar spine BMD vs PBO ($P < 0.001$) • SS ↓ in serum osteocalcin from BL vs PBO ($P < 0.001$)
Raloxifene	Neutral or antagonist[51,54-58] • Meta-analysis of three trials • No difference in thickness by TVU and in incidence of bleeding vs controls • No increase in cancer	Neutral[54,59] • Up to 6-mo CT • No difference in VMV or parabasal, intermediate, or superficial cells by smear vs controls	Antagonist[51] • Meta-analysis of five trials • SS ↓ in all breast cancers ($P < 0.0001$)	Agonist[60,61] • Up to 24-mo RCT • SS ↑ in BMD vs PBO or BL ($P < 0.05$) • SS ↓ in biomarkers of bone turnover vs PBO or BL ($P < 0.05$)
Bazedoxifene (monotherapy)	Antagonist[62] • 7-y RCT • No difference in thickness by TVU and in incidence of hyperplasia vs PBO • SS ↓ in incidence of cancer vs PBO ($P = 0.02$)	Antagonist[63] • 12-wk RCT • Little change in superficial cells vs BL; parabasal cells increased; intermediate cells decreased[c]	Neutral or antagonist [64,65] • 24-mo RCT • No ↑ in density by mammography vs PBO • No difference in cancer rates or pain vs PBO	Agonist[66-68] • Up to 5-y RCT • SS ↓ in incidence of new vertebral fractures vs PBO ($P < 0.05$) • SS ↑ in lumbar spine BMD vs PBO ($P \leq 0.023$) • SS ↓ in serum osteocalcin/CTX vs PBO ($P \leq 0.009$)

Menopause 2014: Vol. 22, No. 7, pp. 786-796

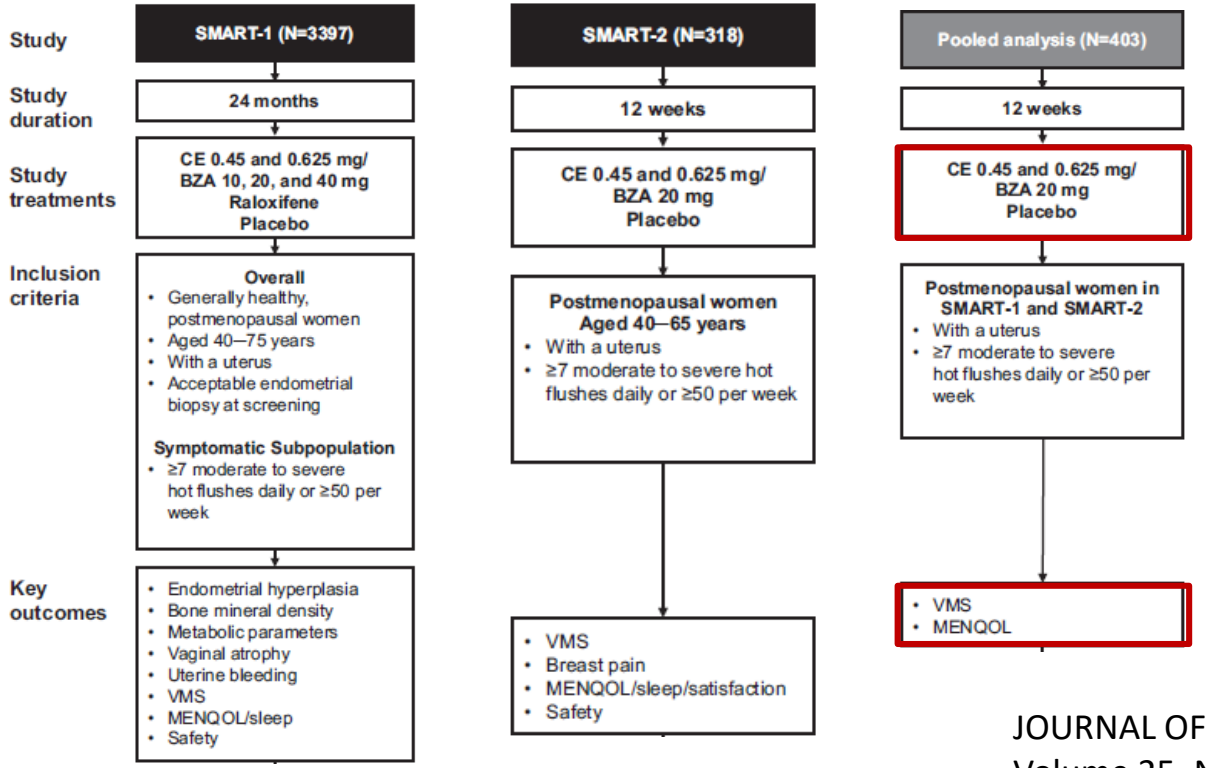
Tissue selective estrogen complex (TSEC)

SERM	Endometrium	Breast	Bone	VMS
Clomiphene[18-20,125]	Antagonist	Antagonist	Agonist	Increase
Tamoxifen[1,7,11,93]	Agonist	Antagonist	Agonist	Increase
Raloxifene[1,23,50,90]	Neutral	Antagonist	Agonist	Increase
Bazedoxifene[1,2,23,24,52,82,95,97,114]	Antagonist	Antagonist	Agonist	Increase
Ospemifene[2,22]	Mixed agonist/antagonist[a]	Antagonist	Agonist	Increase
Toremifene[1,21,126]	Neutral	Antagonist	Agonist	Increase
Lasofoxifene[1,2,23,51,94,107]	Mixed agonist/antagonist	Antagonist	Agonist	Increase
Ormeloxifene[25-29]	Antagonist or weak agonist	Antagonist	Agonist	Not reported

ER, estrogen receptor; SERM, selective estrogen receptor modulator; VMS, vasomotor symptoms.
[a]Ospemifene is an ER agonist in the endometrium at high doses and an antagonist at lower doses

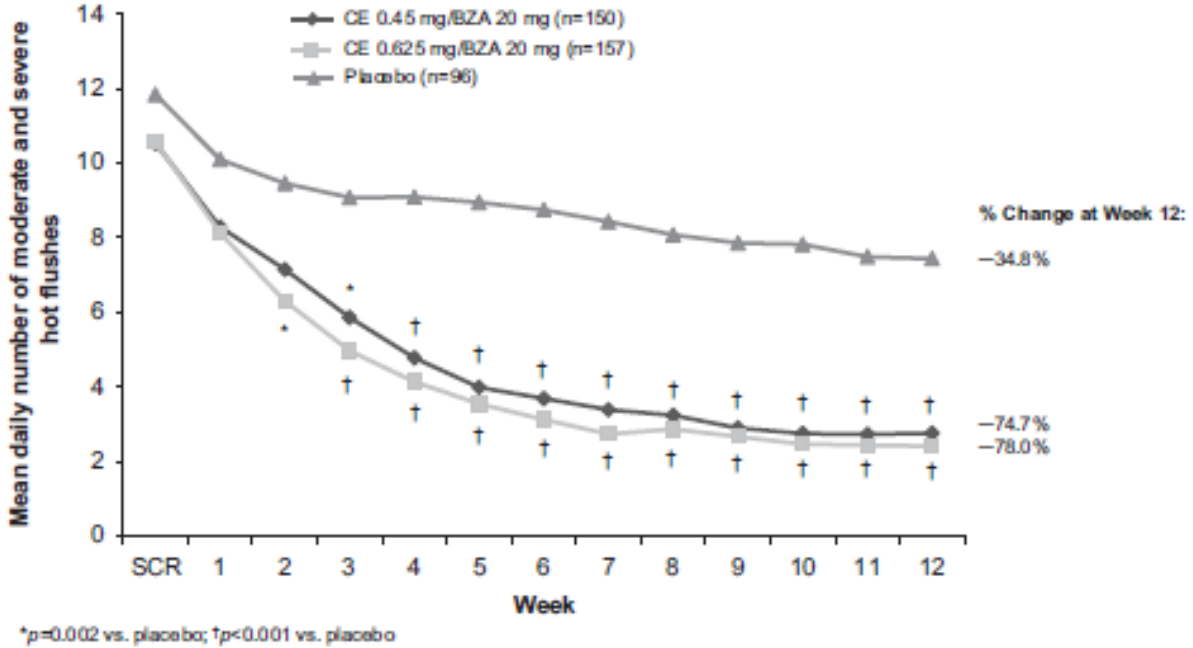
Menopause 2018 Vol. 25, No. 9, pp. 1033-1045

conjugated estrogens/bazedoxifene treatment & vasomotor symptoms



JOURNAL OF WOMEN'S HEALTH
Volume 25, Number 11, 2016: 1102-1111

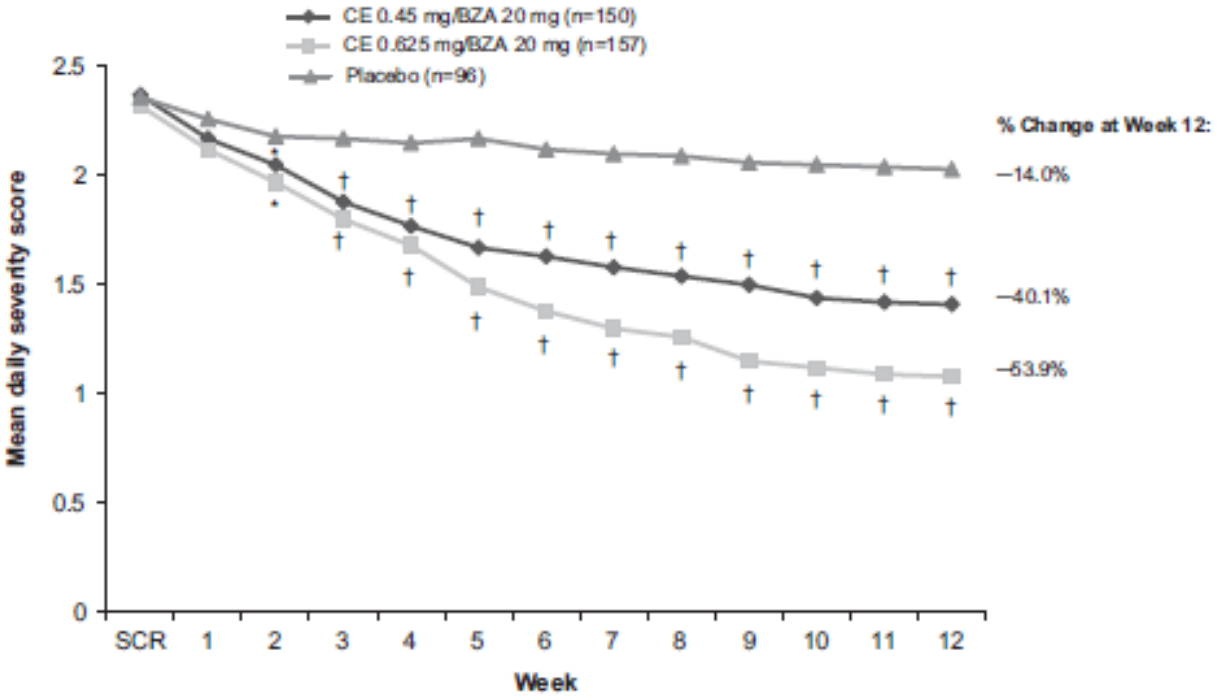
Mean daily number of hot flashes



*p=0.002 vs. placebo; †p<0.001 vs. placebo

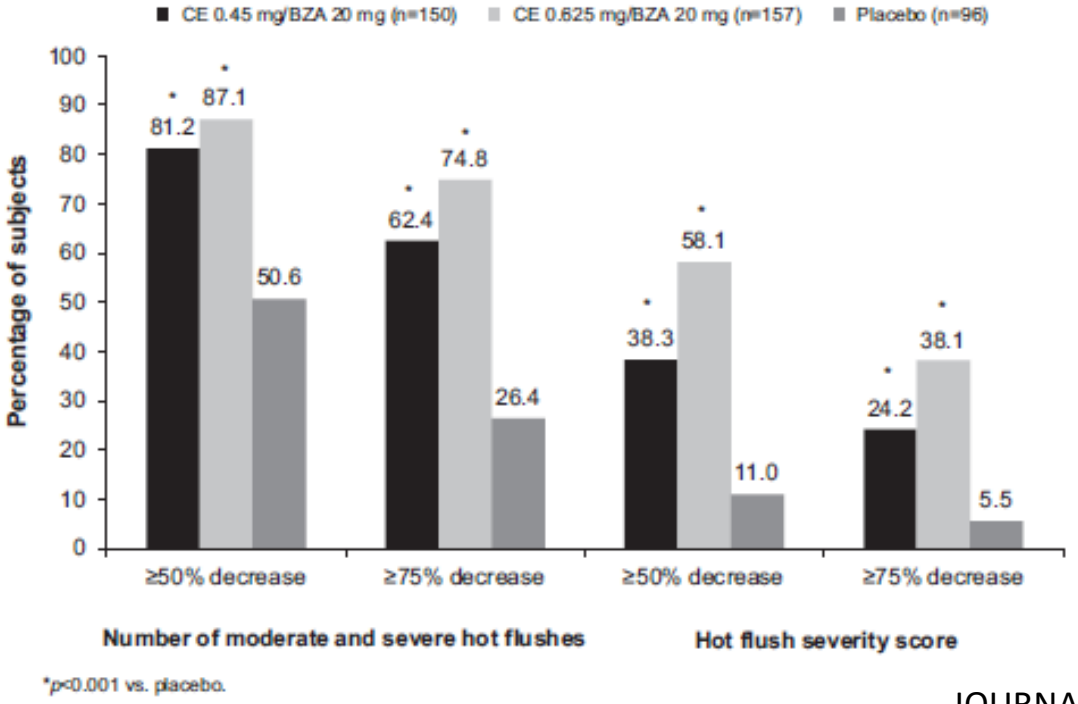
JOURNAL OF WOMEN'S HEALTH
Volume 25, Number 11, 2016: 1102-1111

Mean daily hot flash severity score



*p<0.05 vs. placebo; †p<0.001 vs. placebo

JOURNAL OF WOMEN'S HEALTH
Volume 25, Number 11, 2016: 1102-1111



*$p<0.001$ vs. placebo.

JOURNAL OF WOMEN'S HEALTH
Volume 25, Number 11, 2016: 1102-1111

Effect of years since menopause

Time point	≤5 YSM: CE 0.45 mg/BZA 20 mg (n=92)	≤5 YSM: CE 0.625 mg/BZA 20 mg (n=97)	≤5 YSM: Placebo (n=56)	>5 YSM: CE 0.45 mg/BZA 20 mg (n=58)	>5 YSM: CE 0.625 mg/BZA 20 mg (n=60)	>5 YSM: Placebo (n=40)	p value (Interaction)
Mean change (SE) in average daily number of moderate and severe hot flashes							
Week 4	−5.6 (0.5)	−6.4 (0.5)	−3.7 (0.7)	−6.2 (0.7)	−6.2 (0.6)	−1.2 (0.8)	0.0466
Week 12	−7.6 (0.5)	−8.0 (0.5)	−4.4 (0.6)	−7.9 (0.6)	−7.7 (0.6)	−3.8 (0.8)	0.7427
Mean change (SE) in average daily hot flash severity score							
Week 4	−0.5 (0.1)	−0.6 (0.1)	−0.2 (0.1)	−0.7 (0.1)	−0.6 (0.1)	0.0 (0.1)	0.1166
Week 12	−0.8 (0.1)	−1.1 (0.1)	−0.3 (0.1)	−1.0 (0.1)	−1.3 (0.1)	−0.1 (0.1)	0.0818

SE, standard error; YSM, years since menopause.

JOURNAL OF WOMEN'S HEALTH
Volume 25, Number 11, 2016: 1102-1111

Menopause-specific quality of life

	CE 0.45 mg/BZA 20 mg		*CE 0.625 mg/BZA 20 mg*		*Placebo*	
MENQOL score	n	*Adjusted mean (SE) change*	n	*Adjusted mean (SE) change*	n	*Adjusted mean (SE) change*
Vasomotor function	137	−3.1 (0.2)[a]	137	−3.7 (0.2)[a]	84	−1.4 (0.2)
Psychosocial function	139	−0.8 (0.2)	138	−1.0 (0.2)	84	−0.6 (0.2)
Physical function	139	−1.0 (0.1)	138	−1.3 (0.1)[b]	83	−0.8 (0.1)
Sexual function	138	−1.0 (0.2)	138	−1.3 (0.2)[b]	81	−0.7 (0.2)
Total score	136	−1.5 (0.1)[a]	137	−1.8 (0.1)[a]	81	−0.9 (0.1)

[a] $p < 0.001$ versus placebo.
[b] $p < 0.05$ versus placebo.
MENQOL, menopause-specific quality of life.

JOURNAL OF WOMEN'S HEALTH
Volume 25, Number 11, 2016: 1102-1111

Bazedoxifene & BMD & Fracture

Author	Types of participants	Years since menopause	Age (mean)	Sample size	No. of centers/countries	Types of interventions	Control group	Study duration	Outcome
Itabashi et al. [14]	Postmenopausal women, with an intact uterus, 85 years of age or younger	2	63.43	375 subjects; 311 completed	17 sites in Japan	BZA 20 or 40 mg/day	Placebo	2 years	Change from baseline in BMD of the lumbar spine, incidence of vertebral and non-vertebral fractures
Silverman et al. [19]	Healthy postmenopausal women between the ages of 55 and 85 years with osteoporosis	2	66.40	7492 subjects; 4991 completed	206 sites in Asia-Pacific countries, Canada, Europe, Latin America, South Africa, and the USA	BZA 20 or 40 mg/day	RLX 60 mg/ day or placebo	3 years	Change from baseline in BMD of the lumbar spine, incidence of vertebral and non-vertebral fractures
Silverman et al. [7]	Women who completed the 3-year multicenter outpatient core study.	2	68.97	3146 subjects; 2503 completed	206 sites in Asia-Pacific countries, Canada, Europe, Latin America, South Africa, and the USA	BZA 20 and 40 mg/day	Placebo	2 years	Change from baseline in BMD of the lumbar spine, incidence of vertebral and non-vertebral fractures
Palacios [11]	Women who completed extension I	2	65.7	1530 subjects; 1301 completed	206 sites in Asia-Pacific countries, Canada, Europe, Latin America, South Africa, and the USA	BZA 20 mg/day	Placebo	2 years	Change from baseline in BMD of the lumbar spine, incidence of vertebral, and non-vertebral fractures
Xu et al. '20]	healthy women, 45 years or older without osteoporosis	1	57.24	487 subjects; 450 completed	China, South Korea, and Taiwan	BZA 20 mg/day	Placebo	6 months	Change from baseline in BMD of the lumbar spine

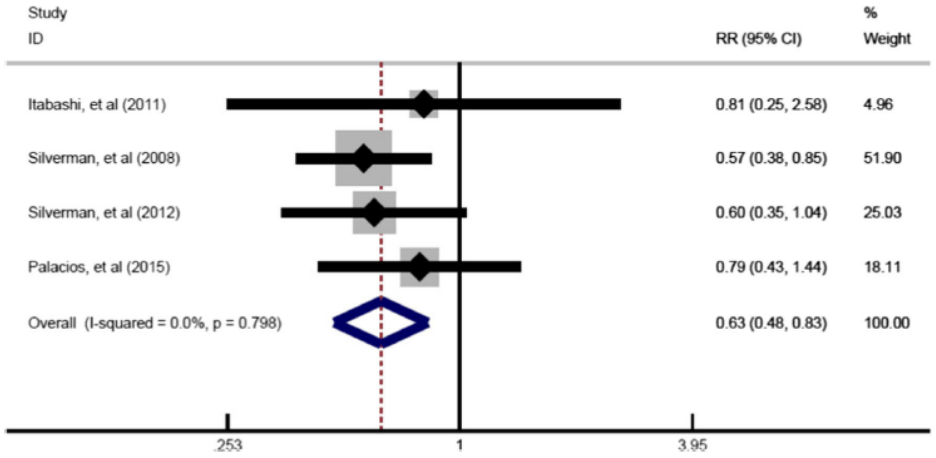
Clinical Reviews in Bone and Mineral Metabolism (2018) 16:22–32

Bazedoxifene & BMD & Fracture

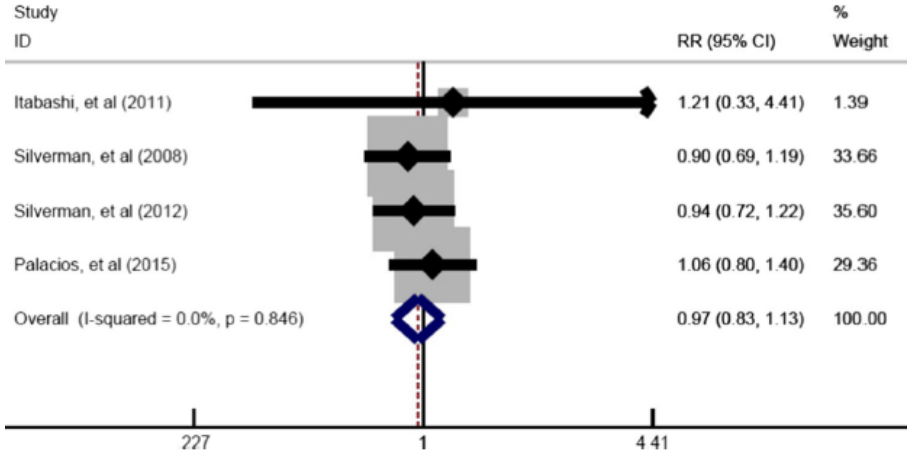
Xu et al. [20]	healthy women, 45 years or older without osteoporosis	1	57.24	487 subjects; 450 completed	China, South Korea, and Taiwan	BZA 20 mg/day	Placebo	6 months	Change from baseline in BMD of the lumbar spine
Miller et al. [16]	healthy women 45 years of age and older	1	57.6	1583 subjects; 1113 completed	101 site in Canada, Europe, and the USA	BZA 20 or 40 mg/day	RLX 60 mg or placebo	2 years	Change from baseline in BMD of the lumbar spine relative to placebo
Lindsay et al. [15]	healthy postmenopausal women aged 40–75 years with an intact uterus	1–5 & more than 5	58.52	3397 subjects; 2315 completed	94 sites in the United States, Europe, and Brazil	BZA (20 or 40 mg/day) each with CE (0.625 or 0.45 mg/day)	RLX 60 mg/day or placebo	2 years	Change from baseline in BMD of the lumbar spine
Mirkin et al. (17)	postmenopausal women aged 40–65 years with an intact uterus	1	54.42	1061 subjects; 850 completed	62 sites in the USA and two sites in Argentina	BZA 20 mg/day and CE 0.45 mg/day or BZA 20 mg/day and CE 0.625 mg/day	CE 0.45 mg/day and MPA 1.5 mg/day or placebo	1 year	Change from baseline in BMD of the lumbar spine
Pinkerton et al. [18]	healthy postmenopausal women aged 40–65 years with an intact uterus	1	54.15	590 subjects; 512 completed	166 sites in the United States, Europe, Australia, New Zealand, Argentina, Chile, Colombia, and Mexico	BZA 20 mg/day and CE 0.45 mg/day or BZA 20 and 0.625 mg/day, BZA 20 mg/day	CE 0.45 mg/day and MPA 1.5 mg/day or placebo	1 year	Change from baseline in BMD of the lumbar spine

Clinical Reviews in Bone and Mineral Metabolism (2018) 16:22–32

BZD 20 mg & vertebral / non-vertebral fractures



Vertebral fracture



Non-vertebral fracture

Clinical Reviews in Bone and Mineral Metabolism (2018) 16:22–32

SMART trials

	SMART-1 [14]	SMART-2 [15]	SMART-3 [16]	SMART-4 [17]	SMART-5 [18]
N (randomized)	3544	332	652	1083	1886
Key eligibility criteria	Postmenopausal women with a uterus				
	Aged 40 to 75 years	Aged 40 to 65 years ≥7 moderate to severe daily hot flushes	Aged 40 to 65 years ≥1 moderate to severe VVA symptoms	Aged 40 to 65 years	Aged 40 to 65 years
Study duration	2 years	12 weeks	12 weeks	1 year (1-year extension)	1 year
Treatments administered (once-daily oral doses)	• CE 0.625 or 0.45 mg each with BZA 10, 20, or 40 mg • Raloxifene 60 mg • Placebo	• CE 0.45 mg/BZA 20 mg • CE 0.625 mg/BZA 20 mg • Placebo	• CE 0.45 mg/BZA 20 mg • CE 0.625 mg/BZA 20 mg • BZA 20 mg • Placebo	• CE 0.45 mg/BZA 20 mg • CE 0.625 mg/BZA 20 mg • CE 0.45 mg/MPA 1.5 mg • Placebo	• CE 0.45 mg/BZA 20 mg • CE 0.625 mg/BZA 20 mg • BZA 20 mg • CE 0.45 mg/MPA 1.5 mg • Placebo
Primary endpoints	• Incidence of endometrial hyperplasia	• Frequency/severity of hot flushes	• Vaginal maturation • Vaginal pH • Most bothersome symptom	• Incidence of endometrial hyperplasia • Bone mineral density	• Incidence of endometrial hyperplasia • Bone mineral density
Secondary endpoints	• Bone mineral density • Bone turnover markers • Frequency/severity of hot flushes • VVA measures • Sleep • Menopause-specific quality of life	• Sleep • Menopause-specific quality of life • Breast pain	• Individual VVA symptoms (dryness, itching/irritation, dyspareunia) • Sexual function • Satisfaction with treatment • Menopause-specific quality of life	• Amenorrhea profile • Breast pain	• Osteoporosis parameters • Bleeding • Breast density • Breast tenderness • Sleep • Menopause-specific quality of life

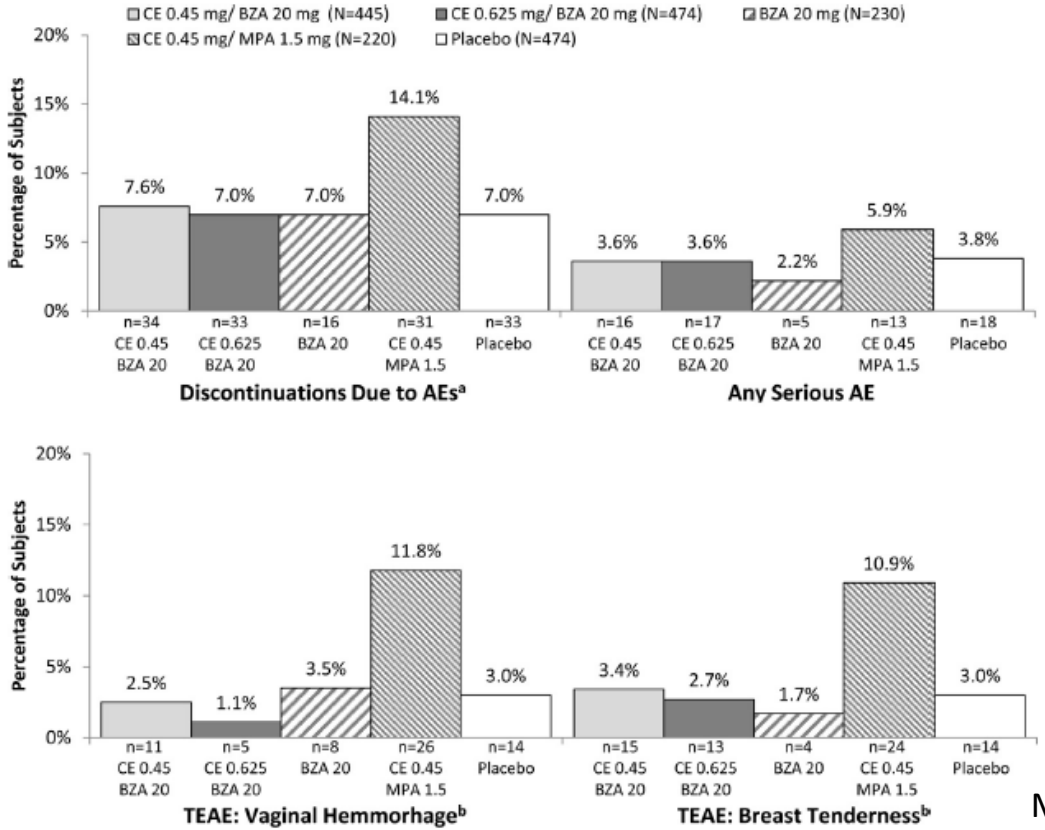
Maturitas 80 (2015) 435–440

Main efficacy results for TSEC from the SMART trials

Study and trial registration	Objective	Main results
SMART 1 NCT00675688 [11]	Effects on menopausal symptoms, metabolic parameters, and overall safety vs. BZA, HT (CE/MPA), and PBO	• Reduction of the moderate-severe daily hot flushes ($p < .05$ vs. PBO) and its severity ($p < .001$ vs. PBO) • Improvements in sleep parameters ($p < .05$ vs. PBO) • Improvements in lipid parameters and homocysteine levels, no changes in carbohydrate metabolism, and only minor effects on some coagulation parameters • Endometrial safety • Breast pain and adverse events similar to placebo
SMART 2 NCT00234819 [12]	Safety and efficacy treating moderate to severe vasomotor symptoms vs. BZA, HT (CE/MPA), and PBO	• Reduction in the number and severity of hot flashes ($p < .001$ vs. PBO) • Improvements in sleep parameters ($p < .05$ vs. PBO) • Improvements in satisfaction and quality of life ($p < .05$ vs. PBO)
SMART 3 NCT00238732 [13]	Efficacy and safety of two doses of TSEC vs. PBO for the treatment of moderate to severe VVA associated with menopause	• Increase in superficial and intermediate cells, and decrease in parabasal cells ($p < .01$ vs. PBO) • Improvements in satisfaction, vasomotor symptoms, sexual function, and quality of life ($p < .05$ vs. PBO)
SMART 4 NCT00242710 [14]	Endometrial safety and BMD effects vs. HT (CE/MPA) and PBO	• Endometrial safety similar to PBO • Bleeding and breast tenderness lower than HT ($p < .05$) • Improve lumbar spine and total hip BMD ($p < .001$ vs. PBO) • Favorable safety/tolerability profile over 1 year
SMART 5 NCT00808132 [15]	Endometrial safety and BMD effects vs. BZA alone, HT, and PBO	• Low endometrial hyperplasia incidence (<1%) in all groups • Cumulative amenorrhea rates similar to PBO and BZA and higher than HT ($p < .001$) • Improve lumbar spine and total hip BMD ($p < .001$ vs. PBO) • Breast tenderness similar to PBO and BZA and significantly lower than HT ($p < .01$) • Adverse event rates were similar among the groups • Serious AEs overall and AE-related discontinuation rates lower than HT

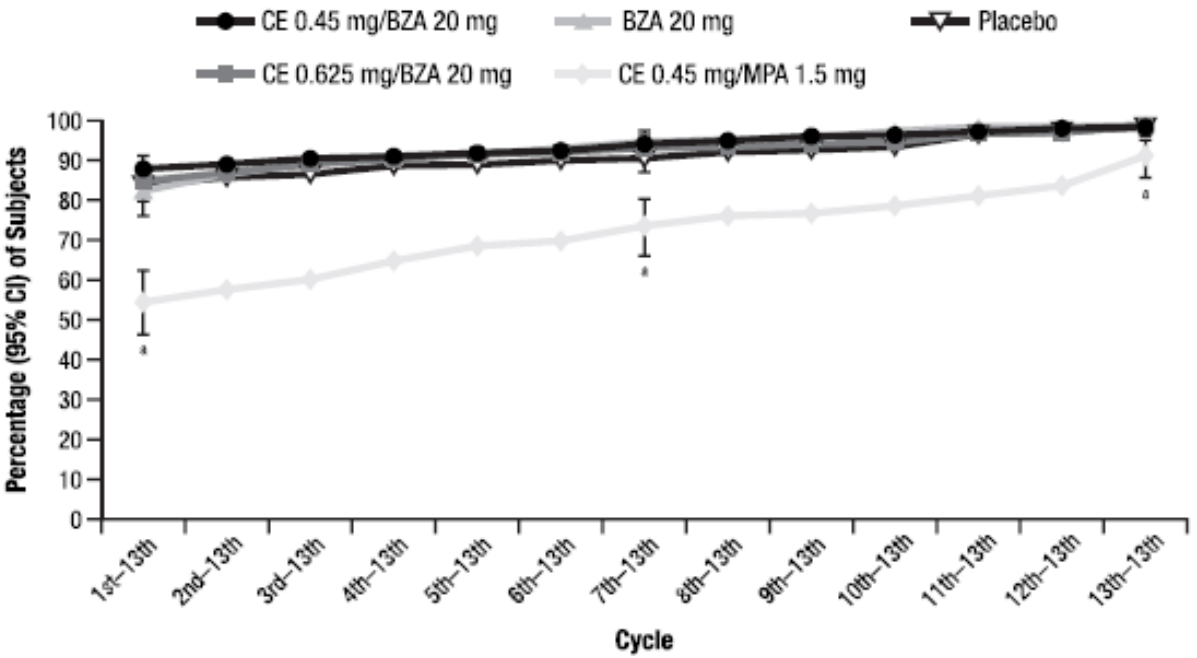
Gynecological Endocrinology, 2018; 34:10, 826-832

Safety and Tolerability



Maturitas 80 (2015) 435–440

Rates of cumulative amenorrhea



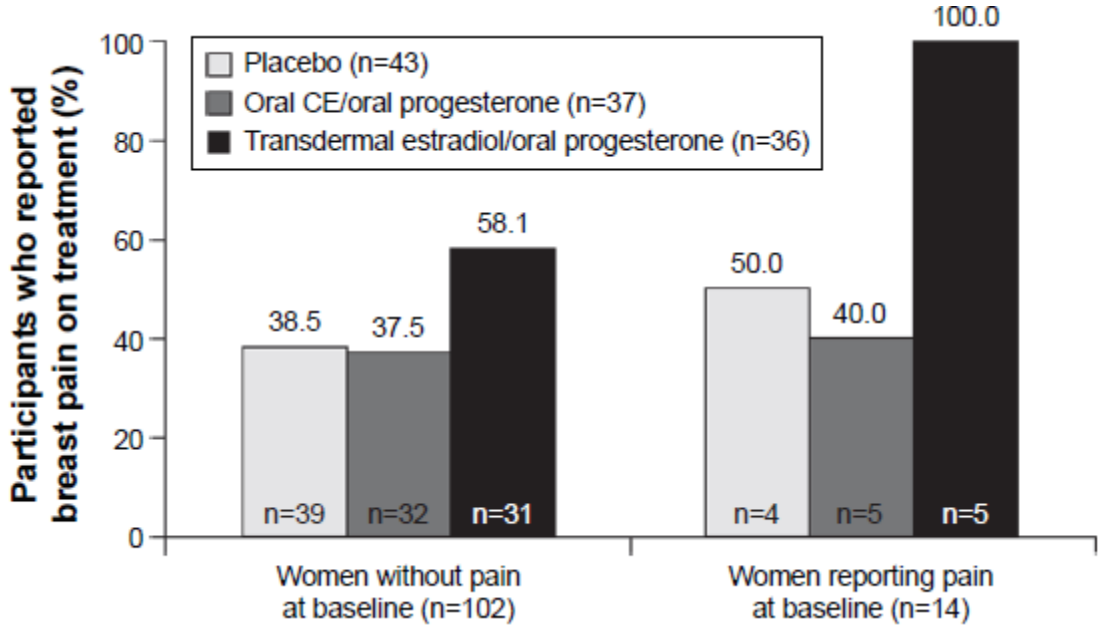
Maturitas 80 (2015) 435–440

Effects of CE/BZD on BMD

	BMD, adjusted mean (SE) percentage change from baseline at month 12			
	CE 0.45 mg/ BZA 20 mg	CE 0.625 mg/ BZA 20 mg	CE 0.45 mg/ MPA 1.5 mg	Placebo
SMART-1 substudy I[a]				
Lumbar spine	1.45 (0.25)*	1.59 (0.25)*	–	–1.14 (0.25)
Total hip	1.06 (0.17)*	1.10 (0.17)*	–	–0.44 (0.17)
Femoral neck	0.65 (0.21)*	0.58 (0.21)*	–	–0.67 (0.21)
Femoral trochanter	1.86 (0.28)*	1.72 (0.28)*	–	–0.09 (0.28)
SMART-1 substudy II[a]				
Lumbar spine	1.08 (0.28)*	1.05 (0.29)*	–	–1.78 (0.29)
Total hip	0.64 (0.20)*	0.26 (0.21)*	–	–0.86 (0.21)
Femoral neck	–0.16 (0.29)**	0.12 (0.30)*	–	–1.27 (0.29)
Femoral trochanter	0.79 (0.27)*	0.85 (0.28)*	–	–1.07 (0.28)
SMART-4				
Lumbar spine	0.80 (0.24)*	0.80 (0.24)*	2.22 (0.37)*	–1.56 (0.35)
Total hip	0.62 (0.19)*	0.84 (0.19)*	1.47 (0.29)*	–0.99 (0.27)
Femoral neck	0.53 (0.24)*	0.69 (0.24)*	0.20 (0.36)*	–1.95 (0.34)
Femoral trochanter	1.20 (0.24)*	1.18 (0.24)*	2.29 (0.36)*	–1.05 (0.34)
SMART-5				
Lumbar spine	0.24 (0.29)*	0.60 (0.27)*	1.30 (0.39)*	–1.28 (0.28)
Total hip	0.50 (0.20)*	0.89 (0.18)*	0.71 (0.26)*	–0.72 (0.18)
Femoral neck	–0.07 (0.26)**	0.84 (0.24)*	0.52 (0.34)*	–1.00 (0.24)
Femoral trochanter	1.31 (0.31)*	1.57 (0.29)*	1.35 (0.41)*	–0.29 (0.29)

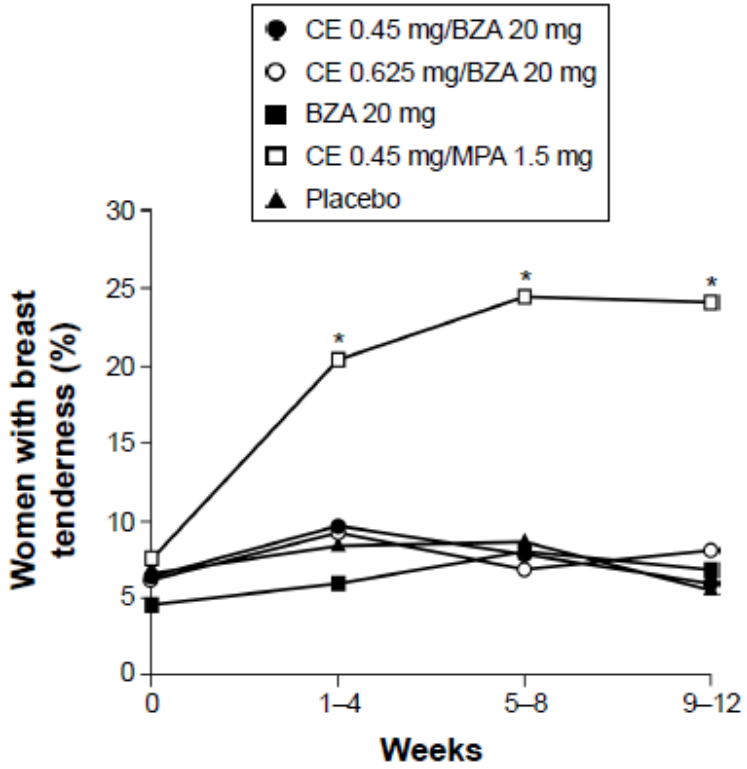
Therapeutics and Clinical Risk Management 2016:12 549–562

Breast pain during treatment



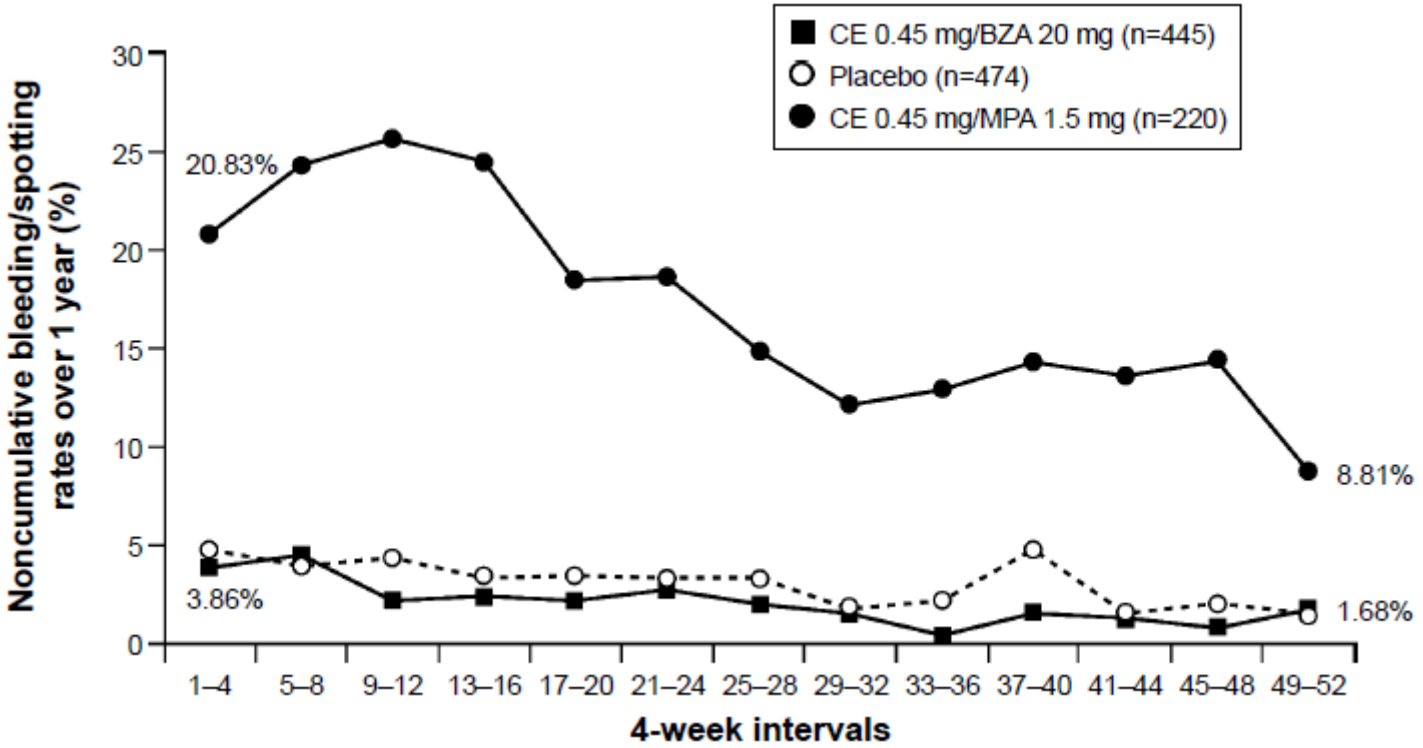
Therapeutics and Clinical Risk Management 2016:12 549–562

Breast tenderness in daily diaries



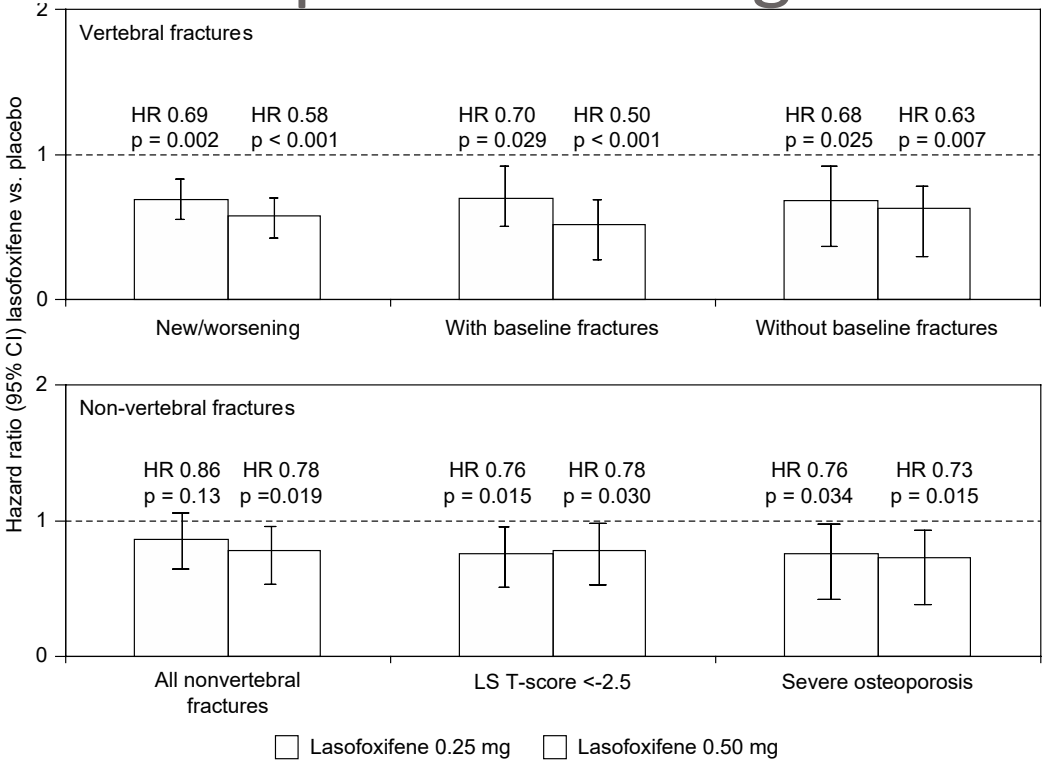
Therapeutics and Clinical Risk Management 2016:12 549–562

Bleeding/ spotting



Therapeutics and Clinical Risk Management 2016:12 549–562

a new selective estrogen receptor modulator for the treatment of osteoporosis and vaginal atrophy



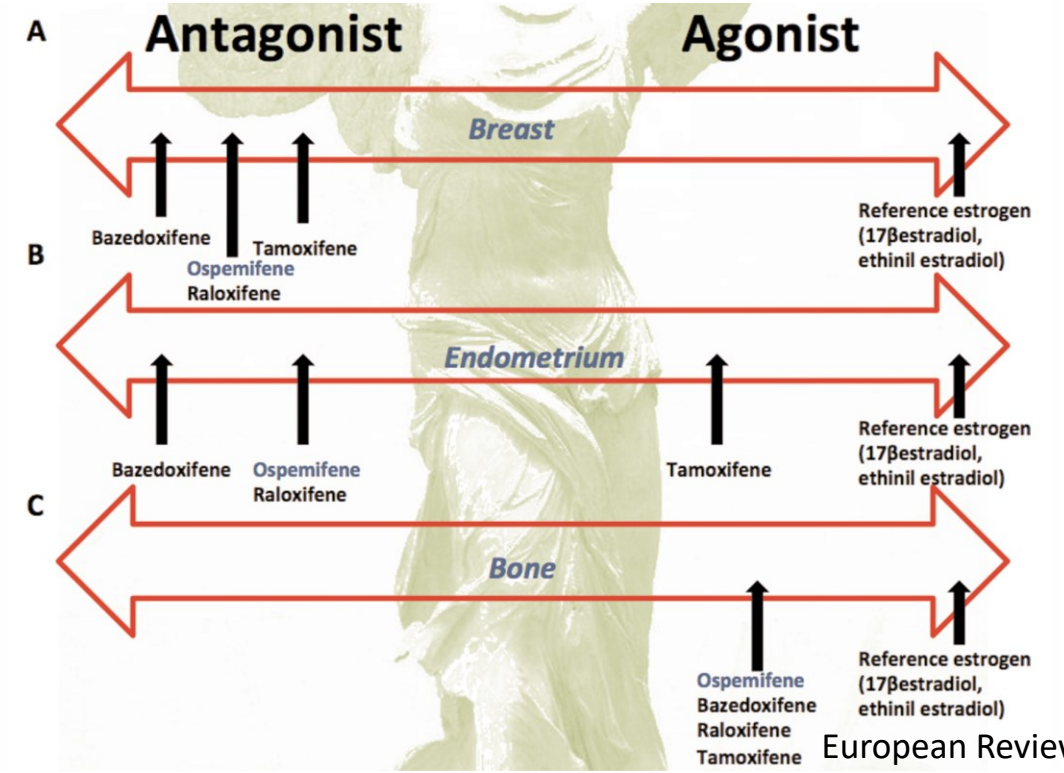
Expert Opin. Pharmacother. (2009) 10(13):2209-2220

Compounds whose development has been suspended

- Lasofoxifene (= desmethyl dihydro analogue of nafoxidine): FDA registration for osteoporosis refused in 2005. In 2009 EU marketing authorization for the treatment of osteoporosis. Marketing authorization is no longer valid as a result of the “Sunset Clause”. The rights to lasofoxifene have recently been acquired by Sermonix Pharmaceuticals LLC with a view to restarting the development. J Reproduktions med Endokrinol_Online 2015; 12 (4)
- Although several studies have found that lasofoxifene resulted in significant improvements in vaginal pH and vaginal maturation index, clinical development of this SERM is on hold.

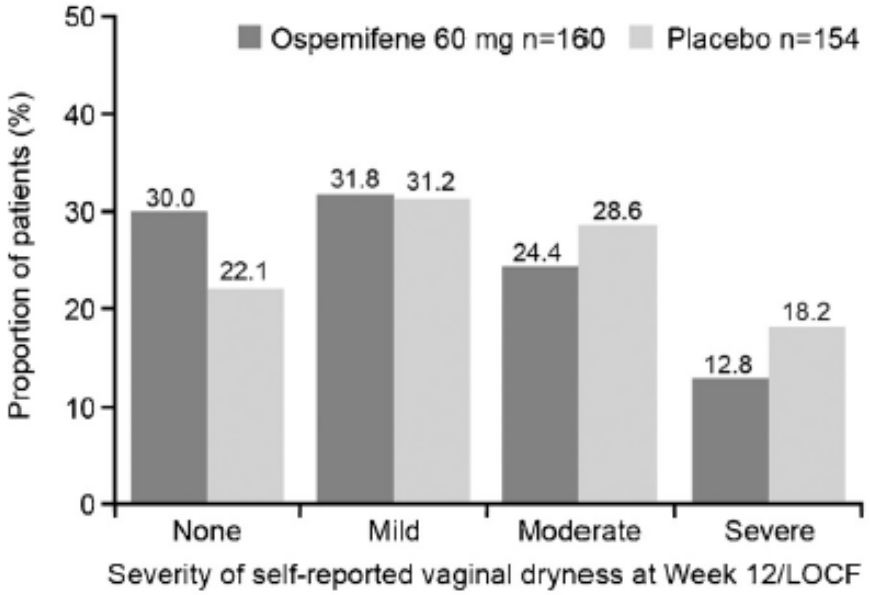
Journal of Menopausal Medicine 2015;21:65-71

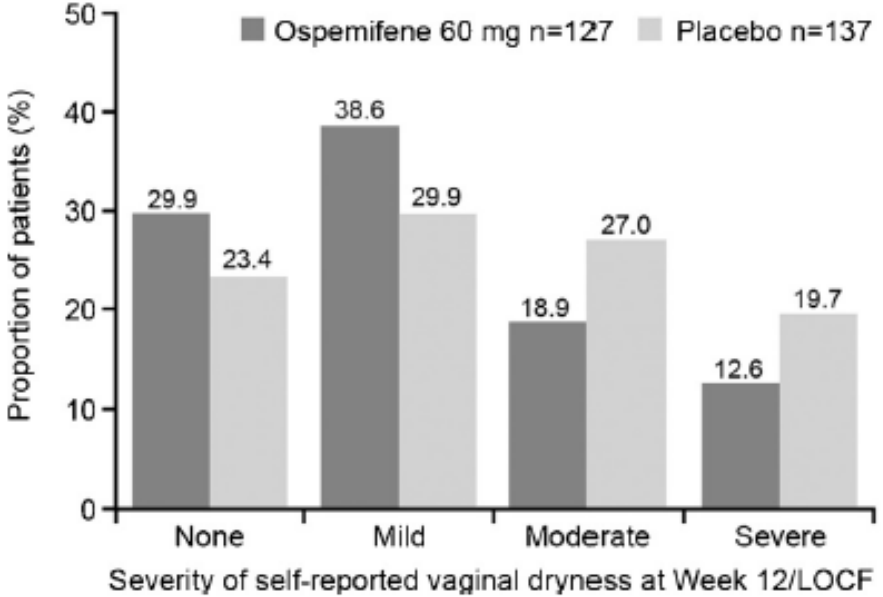
Strenght of the antagonist and agonist effect of ospemifene compared with other SERMS



European Review for Medical and Pharmacological Sciences 2016; 20: 3934-3944

A non-estrogen selective estrogen receptor modulator
Intention to treat population / per protocol population

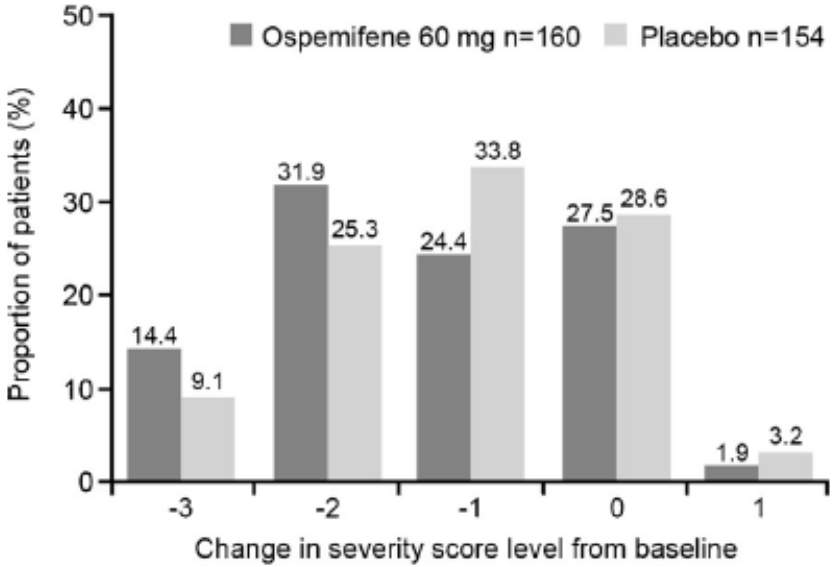


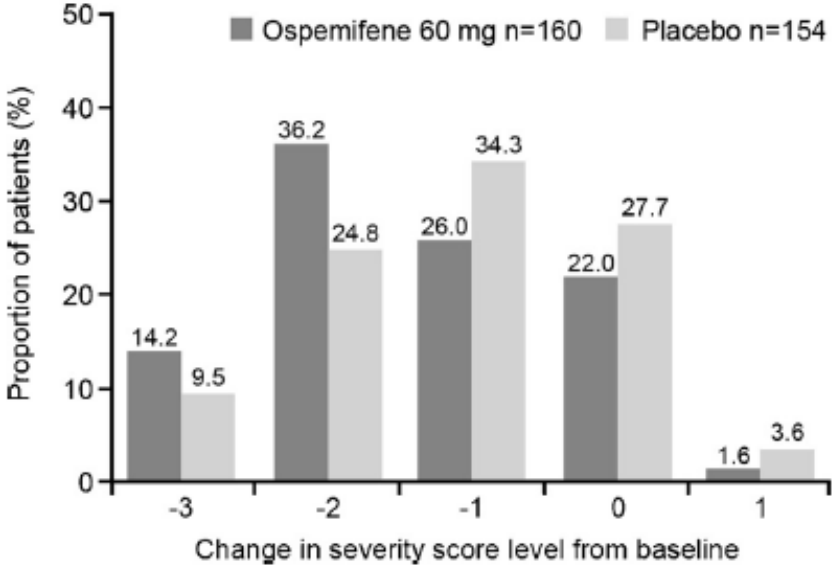


The intent-to-treat (ITT) population, which consisted of all randomised participants who took at least one dose of the study medication.
The per-protocol (PP) population completed at least 10 weeks of treatment, took ≥85% of the study medication and did not have any other major protocol violation, vaginal infection or any other medical condition that would confound the primary efficacy assessment.

Maturitas 78 (2014) 91–98

Intention to treat population / per protocol population

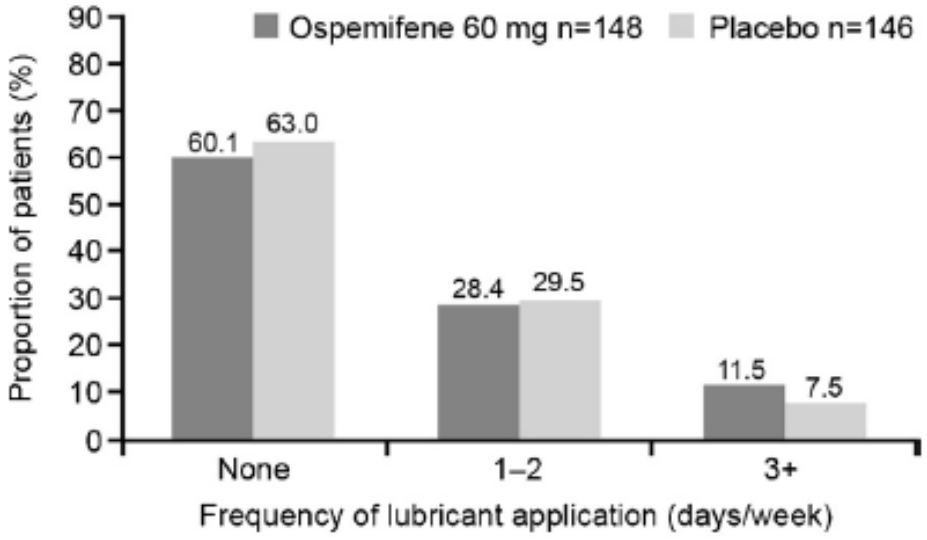


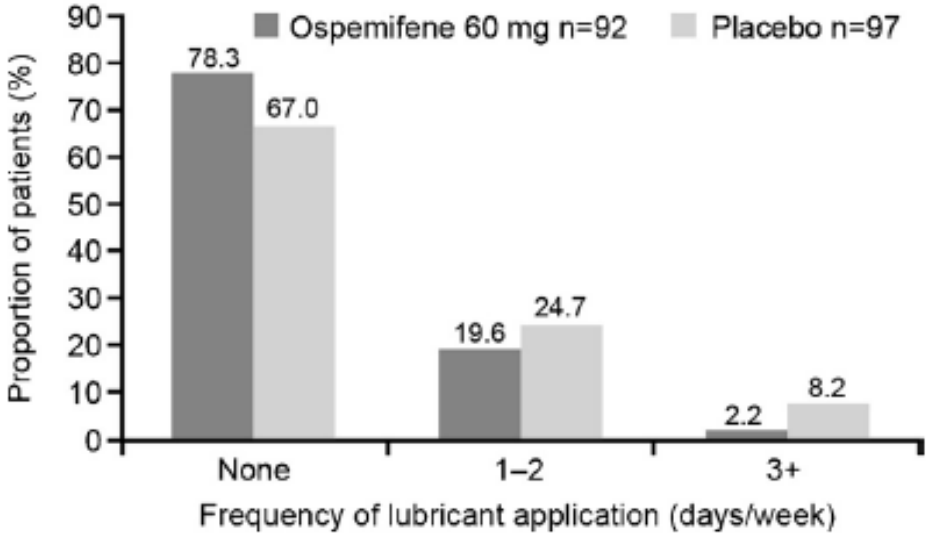


Change from baseline was determined as
−3 being a change from ‘severe’ to ‘none’;
−2 being either a change from ‘severe’ to ‘mild’ or from ‘moderate’ to ‘none’;
−1 being either ‘severe’ to ‘moderate’, ‘moderate’ to ‘mild’, or ‘mild’ to ‘none’, and zero being no change.
A change of 1 indicated a change from ‘moderate’ to ‘severe’, ‘mild’ to ‘moderate’, or ‘none’ to ‘mild’.

Maturitas 78 (2014) 91–98

Week 1 / Week 12





Maturitas 78 (2014) 91–98

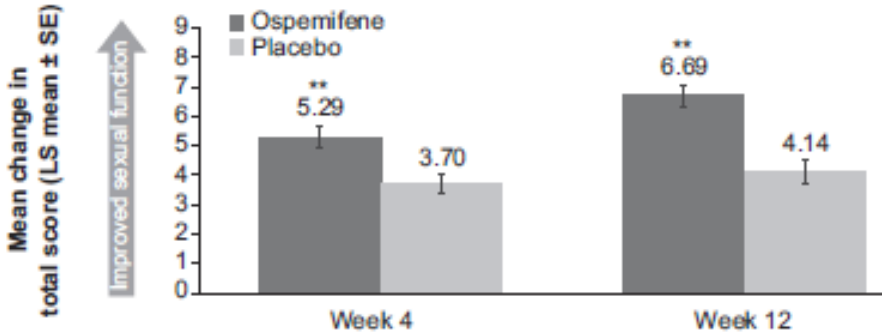
Female Sexual Function Index

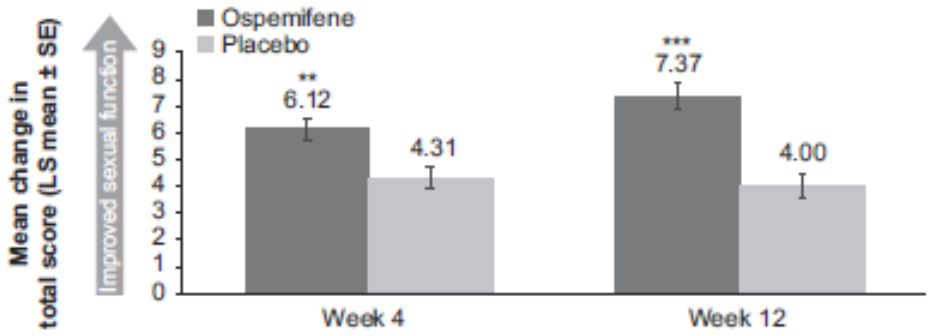
Table 1 Female Sexual Function Index scoring system. A domain score of zero indicates that no sexual activity was reported during the past month. From: Rosen R, *et al. J Sex Marital Ther* 2001;26:191–208. Available at http://www.fsfi-questionnaire.com/

Domain	*Questions*	*Score range*	*Factor*	*Minimum score*	*Maximum score*
Desire	1, 2	1–5	0.6	1.2	6
Arousal	3, 4, 5, 6	0–5	0.3	0	6
Lubrication	7, 8, 9, 10	0–5	0.3	0	6
Orgasm	11, 12, 13	0–5	0.4	0	6
Satisfaction	14, 15, 16	0 (or 1)–5	0.4	0	6
Pain	17, 18, 19	0–5	0.4	0	6
Full scale score range				2	36

Climacteric 2015; 18:2, 226-232

Total score
Intention to treat population / dyspareunia

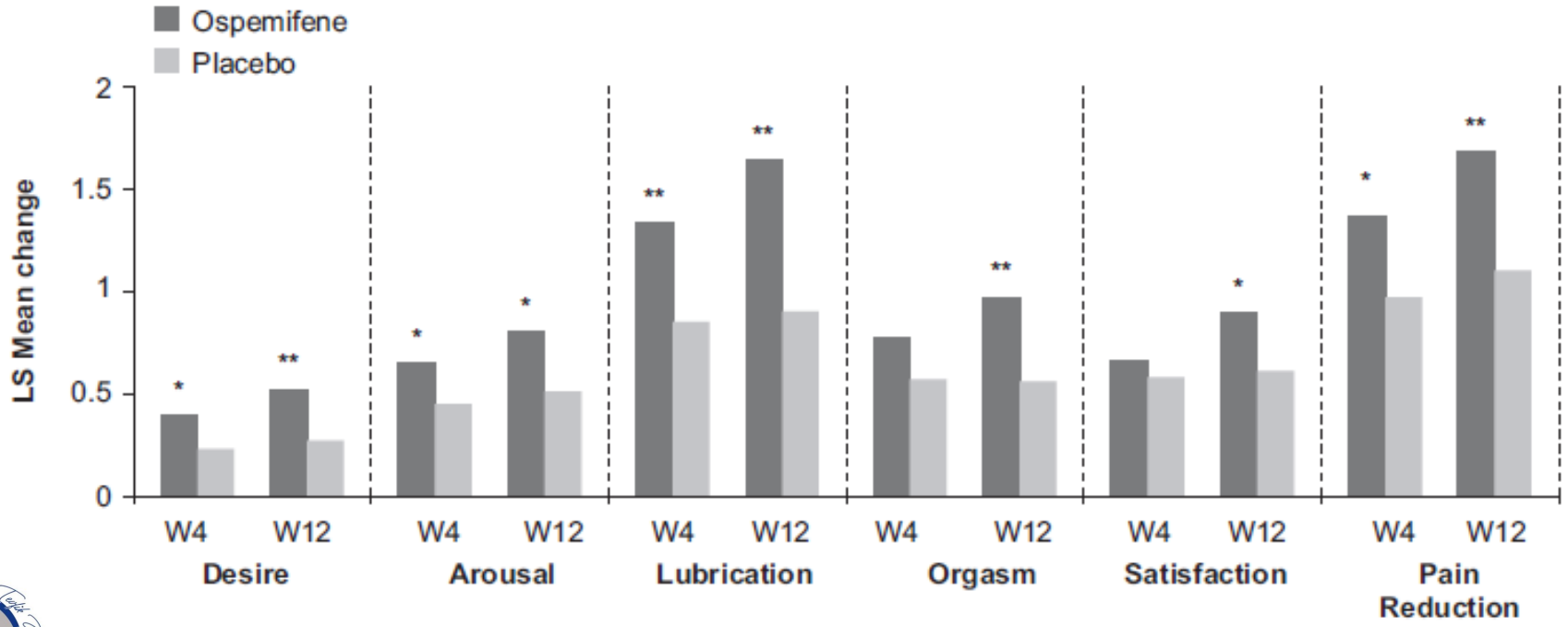




ITT - all randomized subjects who had received > one dose of the study medication

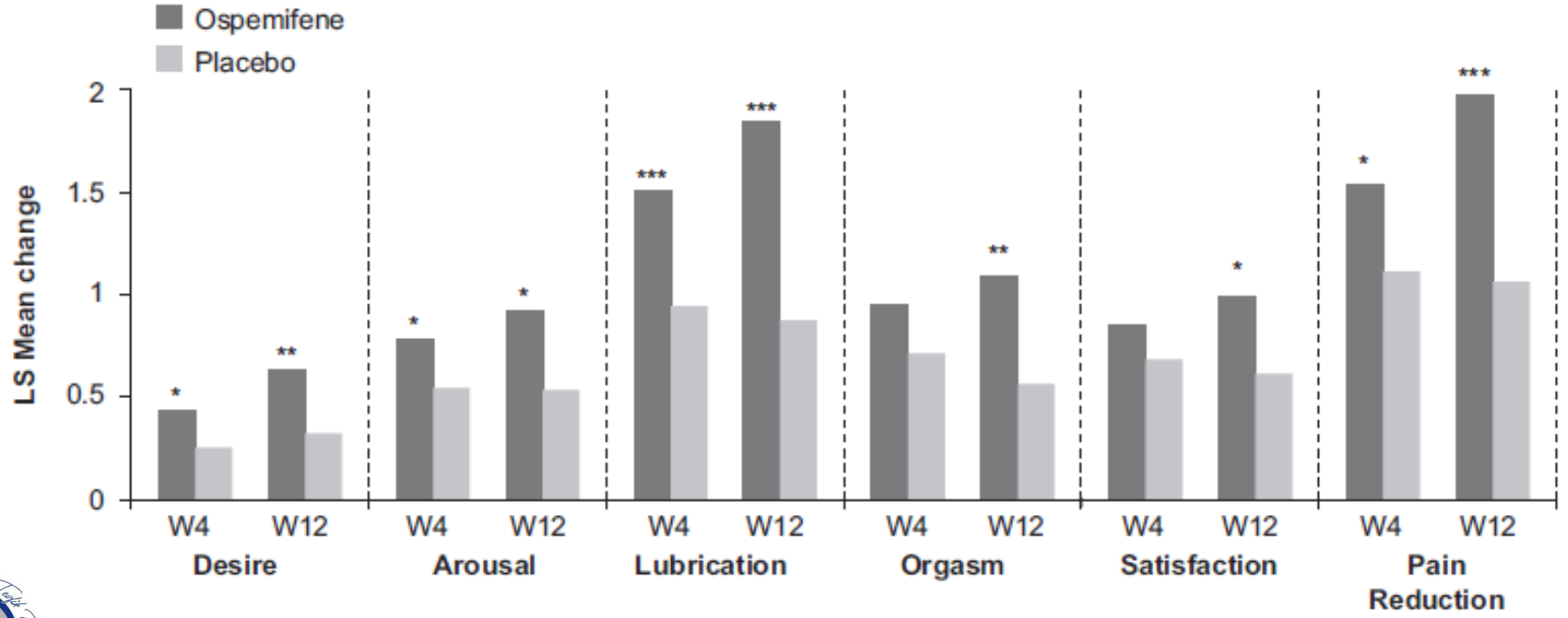
Climacteric 2015; 18:2, 226-232

Intention to treat population



Climacteric 2015; 18:2, 226-232

dyspareunia



Climacteric 2015; 18:2, 226-232

Overall Safety of Ospemifene in Postmenopausal Women from Placebo-Controlled Phase 2 and 3 Trials

Study no.	*Study design*	*Study duration*	*Treatment administered*	*Inclusion criteria*	*Efficacy endpoints*
15-50717	Phase 2, placebo-controlled	12 weeks	Ospemifene 5 mg/day ($n=98$) 15 mg/day ($n=98$) 30 mg/day ($n=98$) Placebo ($n=98$)	Postmenopausal women (40–80 years) with BMI <37 kg/m^2 diagnosed with VVA	Primary • Change from baseline to week 12 in % parabasal cells, % superficial cells, and vaginal pH Secondary • Change from baseline to weeks 4 and 12 in visual evaluation of vagina • Change from baseline to week 4 in % parabasal cells, % superficial cells, and vaginal pH • Change from baseline to weeks 4 and 12 in serum hormone levels
15-50615[22]	Phase 2, placebo-controlled	6 weeks	Ospemifene 60 mg/day ($n=100$) Placebo ($n=98$)	Postmenopausal women (40–70 years) with ≥7 moderate to very severe hot flush per day or 50 per week	Primary • Change in frequency and severity of moderate to very severe hot flush from baseline to week 6 Secondary • Change in frequency and severity of mild to very severe hot flush from baseline to week 6
1506002[30]	Phase 2, placebo-controlled	12 weeks	Ospemifene 30 mg/day ($n=40$) 60 mg/day ($n=40$) 90 mg/day ($n=40$) Placebo ($n=40$)	Healthy, postmenopausal women (45–65 years) with BMI ≤30 kg/m^2	Primary • Biochemical markers for bone turnover from baseline to 12 weeks • Change in Kupperman index and single climacteric symptoms from baseline to weeks 4 and 12 Secondary • Change from baseline to week 12 in lipid/coagulation factors, endometrial biopsy and thickness, and glucose tolerance

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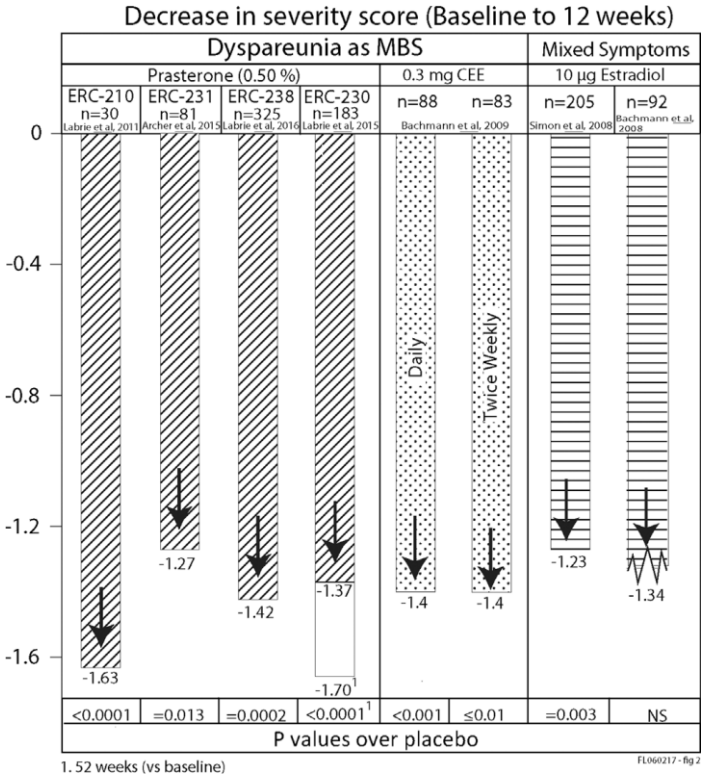
Phase 3, placebo-controlled	12 weeks	Ospemifene 60 mg/day (n =463) Placebo (n =456)	Postmenopausal women (40–80 years) with BMI <37 kg/m^2, and diagnosed with VVA and self-reported MBS of either dyspareunia or vaginal dryness	Primary • Change from baseline to week 12 in % parabasal cells, % superficial cells, vaginal pH, and severity of MBS Secondary • Change from baseline to week 4 in % parabasal cells, % superficial cells, vaginal pH, and severity of MBS • Responder analysis at week 12 • Change in sexual activity and lubricant use from baseline to weeks 1 and 12	

Study no.	*Study design*	*Study duration*	*Treatment administered*	*Inclusion criteria*	*Efficacy endpoints*
15-50310[15]/ 15-50310x[20a]	15-50310: Phase 3, placebo-controlled	12 weeks	Ospemifene 30 mg/day (n =282) 60 mg/day (n =276) Placebo (n =268)	Postmenopausal women (40–80 years) with BMI <37 kg/m^2, diagnosed with VVA and either dyspareunia or vaginal dryness as the self-reported MBS	Primary • Change from baseline to week 12 in % parabasal cells, % superficial cells, vaginal pH, and severity of MBS Secondary • Change from baseline to week 4 in % parabasal cells, % superficial cells, vaginal pH, and severity of MBS; lubricant use
	15-50310x: Phase 3, placebo-controlled, safety study	40 weeks extension	Ospemifene 30 mg/day (n =62) 60 mg/day (n =69) Placebo (n =49)	Postmenopausal women from study 15-50310 with an intact uterus	Only safety assessments conducted
15-50718[21]	Phase 3, placebo-controlled safety study	52 weeks	Ospemifene 60 mg/day (n =363) Placebo (n =63)	Postmenopausal women (40–80 years) with an intact uterus, BMI <30 kg/m^2, diagnosed with VVA, and either dyspareunia or vaginal dryness as the self-reported MBS	Primary • Change from baseline to week 12/LOCF in % parabasal cells, % superficial cells, and vaginal pH Secondary • Changes from baseline to weeks 12, 26, and 52 in % parabasal cells and % superficial cells, vaginal pH, visual evaluation of the vagina, and serum hormone levels

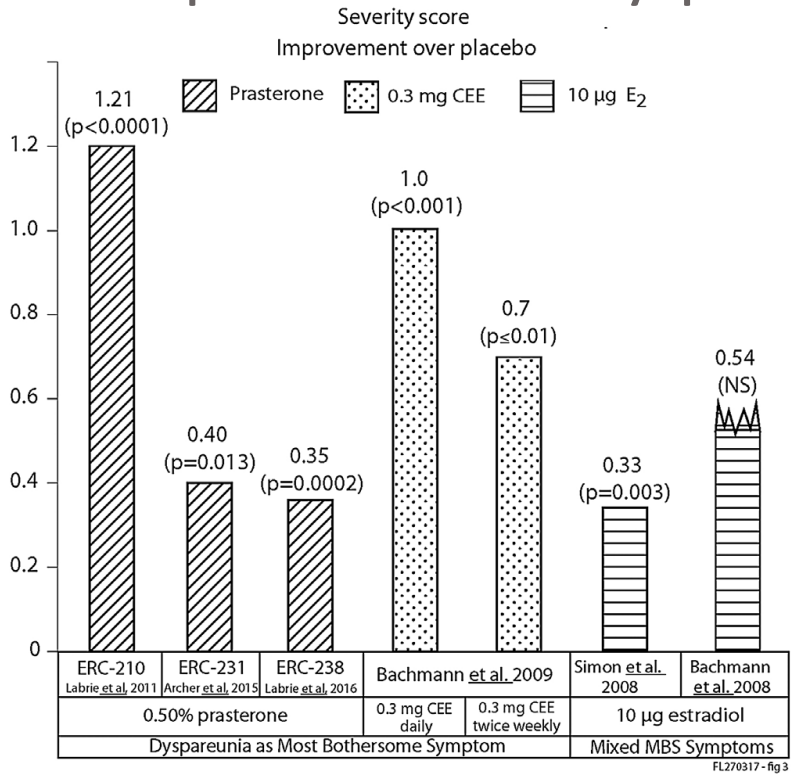
JOURNAL OF WOMEN'S HEALTH, 2017

Comparison of the Effect of Intravaginal 6.5 mg (0.50%) DHEA (Prasterone), 0.3 mg Conjugated Equine Estrogens and 10 µg Estradiol on the Decrease of Severity of Dyspareunia.



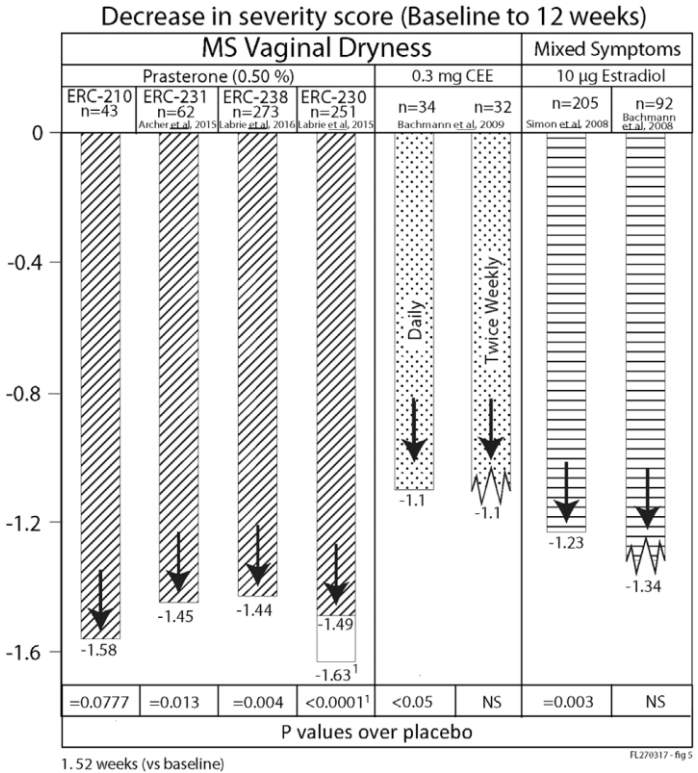
Journal of Steroid Biochemistry and Molecular Biology 174 (2017) 1–8

Comparison of the Effect of Intravaginal 6.5 mg (0.50%) DHEA (Prasterone), 0.3 mg Conjugated Equine Estrogens and 10 µg Estradiol on the Improvement of Dyspareunia Over Placebo



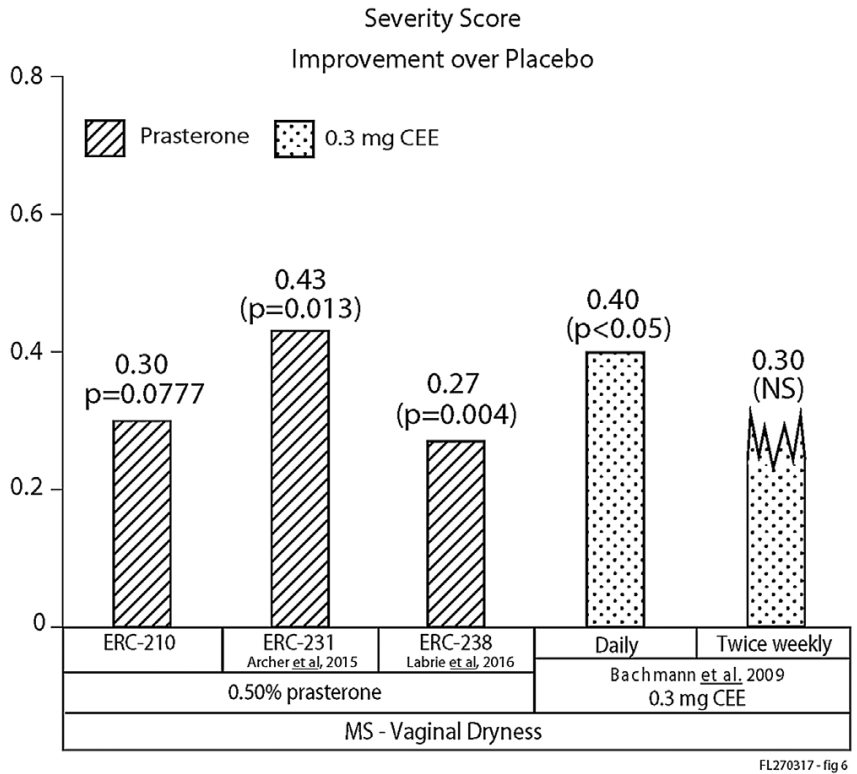
Journal of Steroid Biochemistry and Molecular Biology 174 (2017) 1–8

Comparison of the Effect of Intravaginal 6.5 mg (0.50%) DHEA (Prasterone), 0.3 mg Conjugated Equine Estrogens and 10 µg Estradiol on the Decrease of Severity of Vaginal Dryness



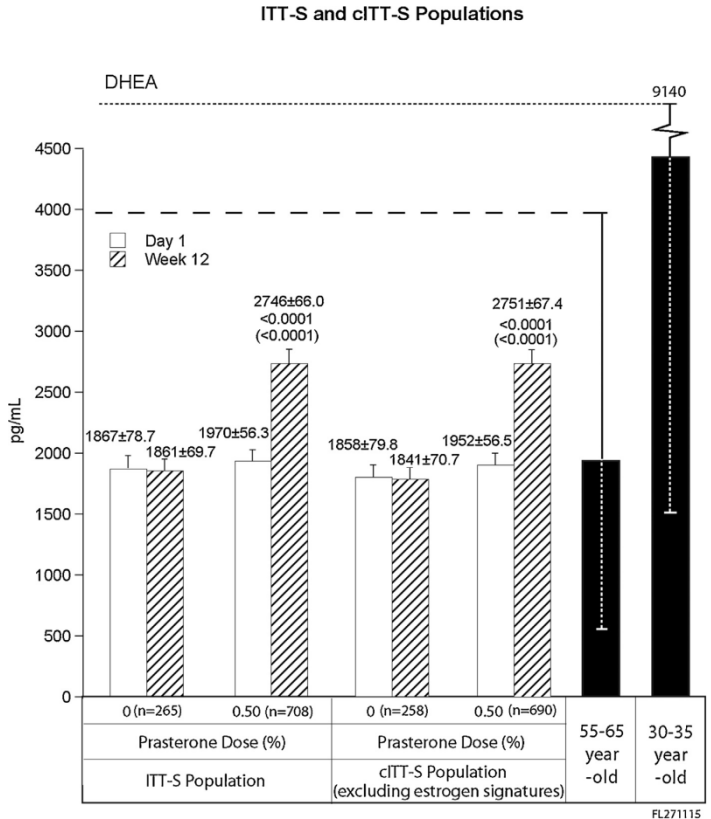
Journal of Steroid Biochemistry and Molecular Biology 174 (2017) 1–8

Comparison of the Effect of Intravaginal 6.5 mg (0.50%) DHEA (Prasterone) and 0.3 mg Conjugated Equine Estrogens on the Improvement of Vaginal Dryness Over Placebo



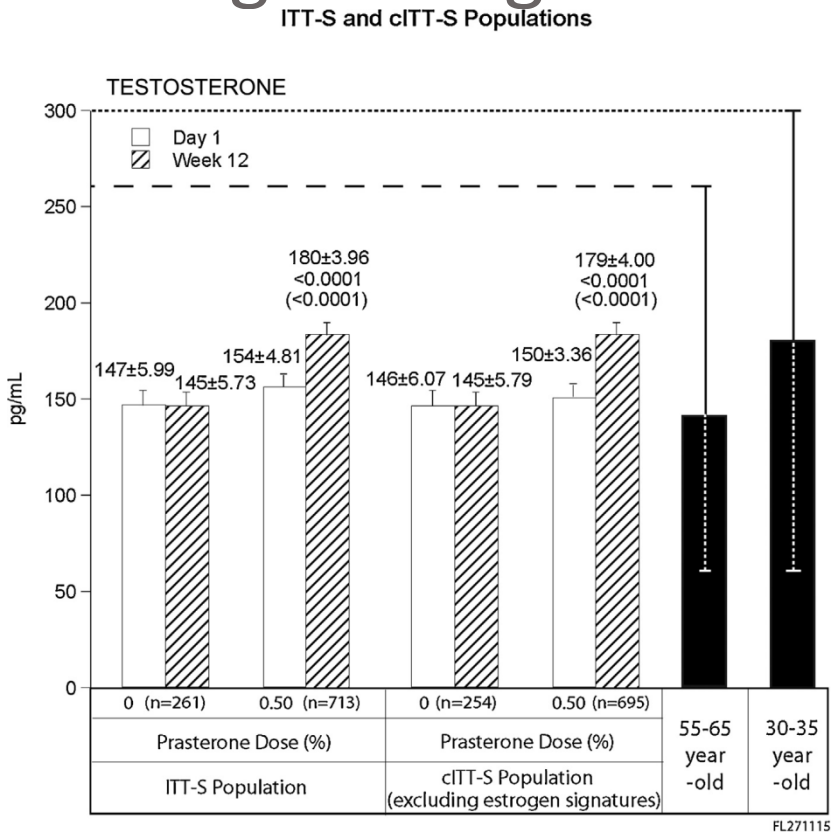
Journal of Steroid Biochemistry and Molecular Biology 174 (2017) 1–8

Serum DHEA remains well within normal postmenopausal values following intravaginal 0.50% DHEA



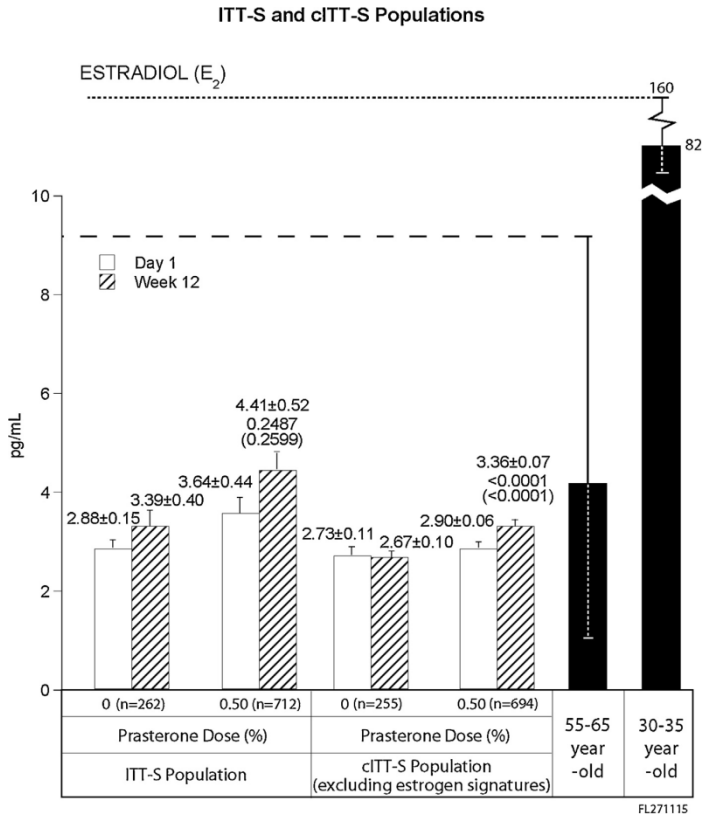
Journal of Steroid Biochemistry & Molecular Biology 159 (2016) 142–153

Serum testosterone shows no biologically significant change following intravaginal 0.50% DHEA



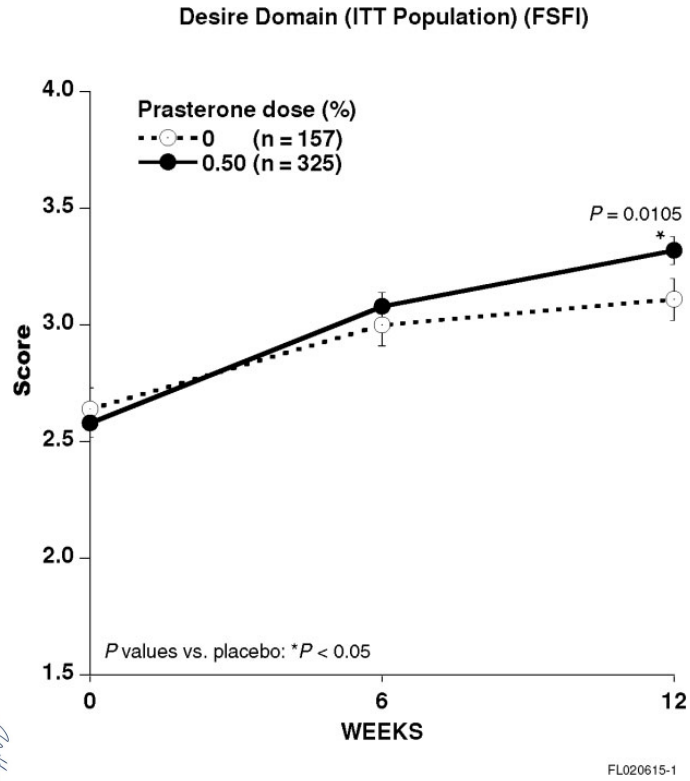
Journal of Steroid Biochemistry & Molecular Biology 159 (2016) 142–153

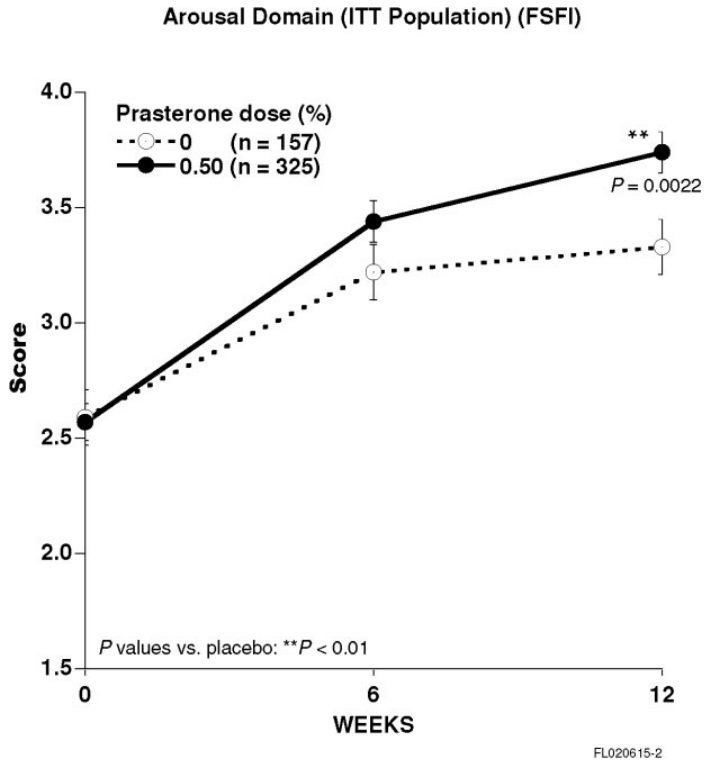
Serum estradiol remains well within normal postmenopausal values following intravaginal 0.50% DHEA



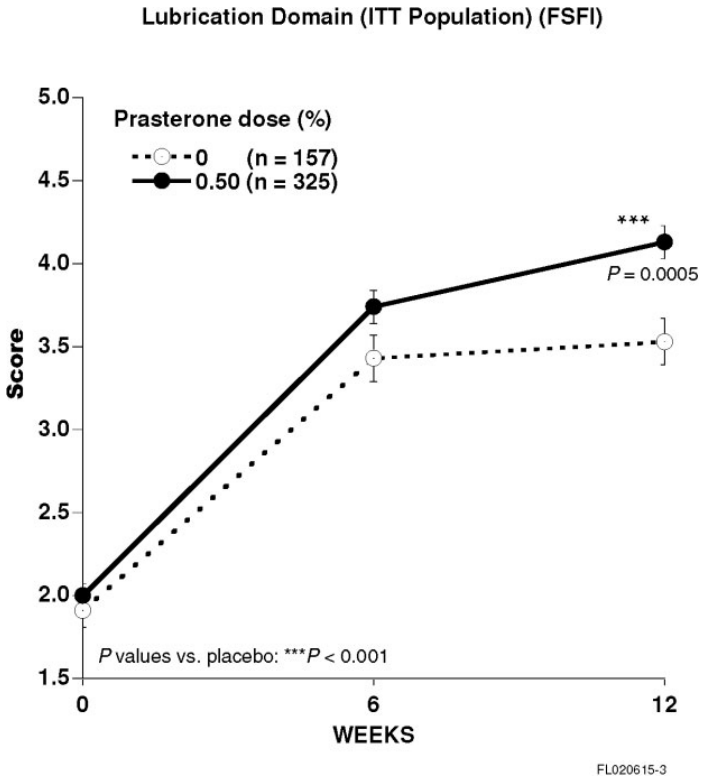
Journal of Steroid Biochemistry & Molecular Biology 159 (2016) 142–153

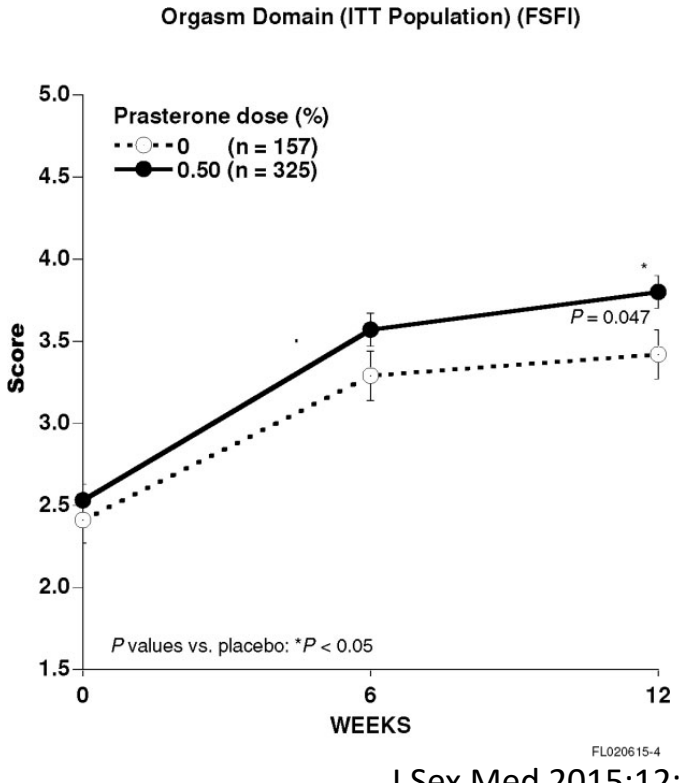
Effect of Intravaginal Prasterone on Sexual Dysfunction





J Sex Med 2015;12:2401–2412





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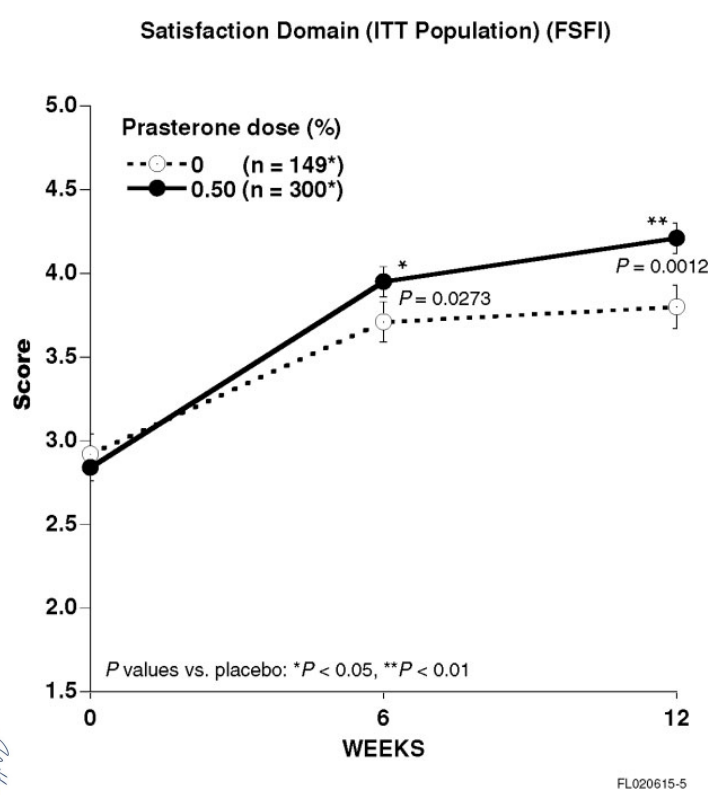
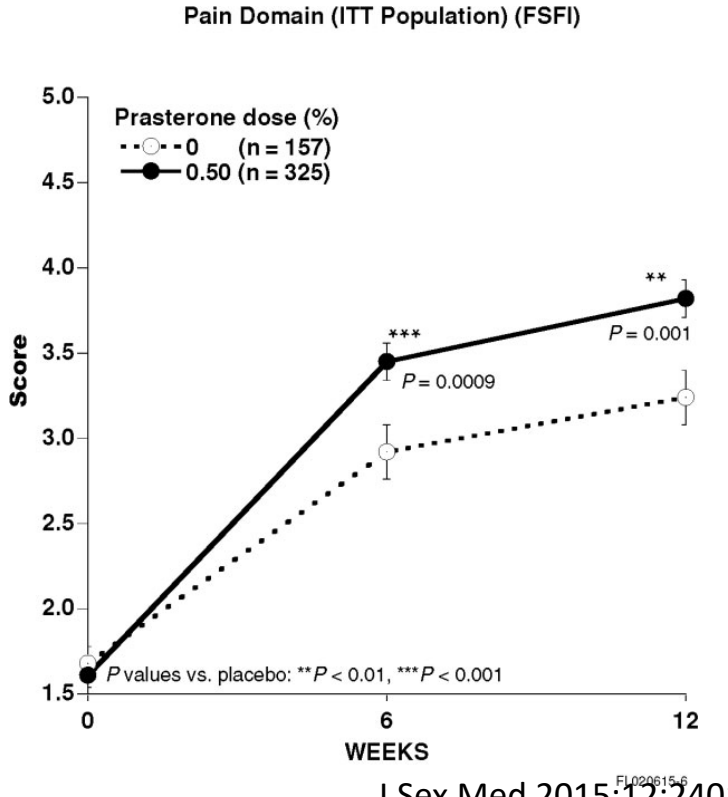
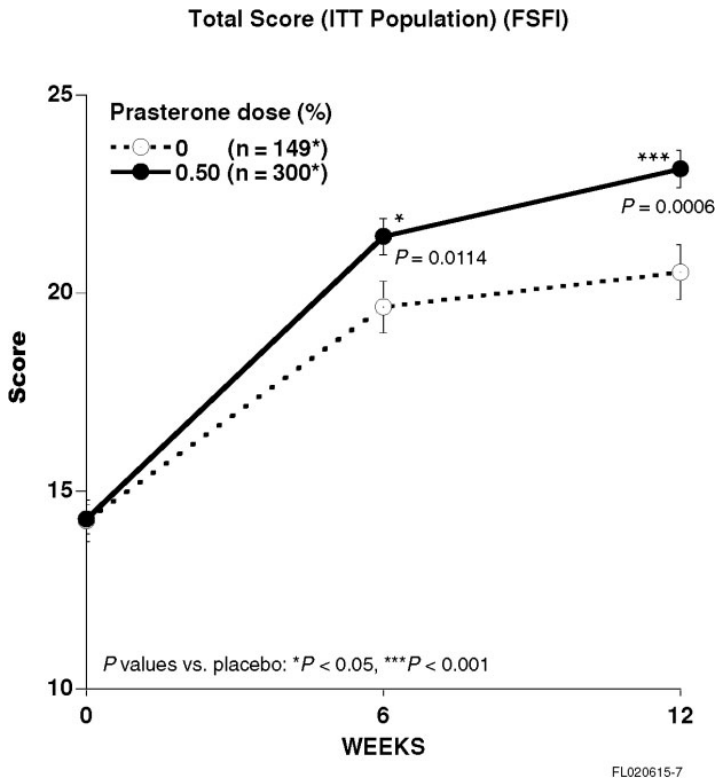


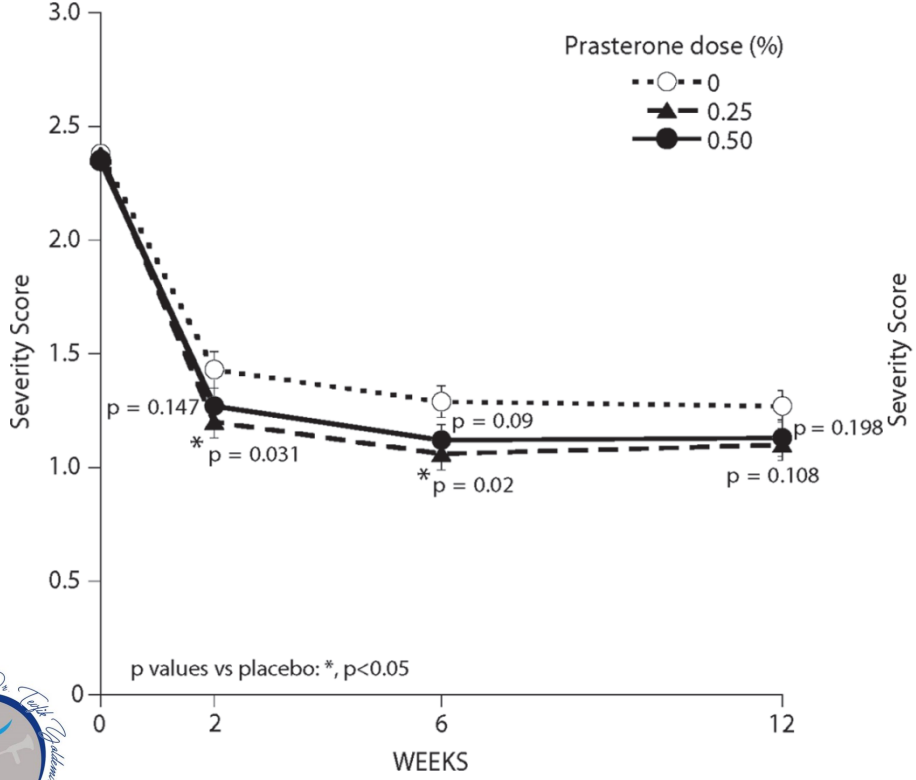


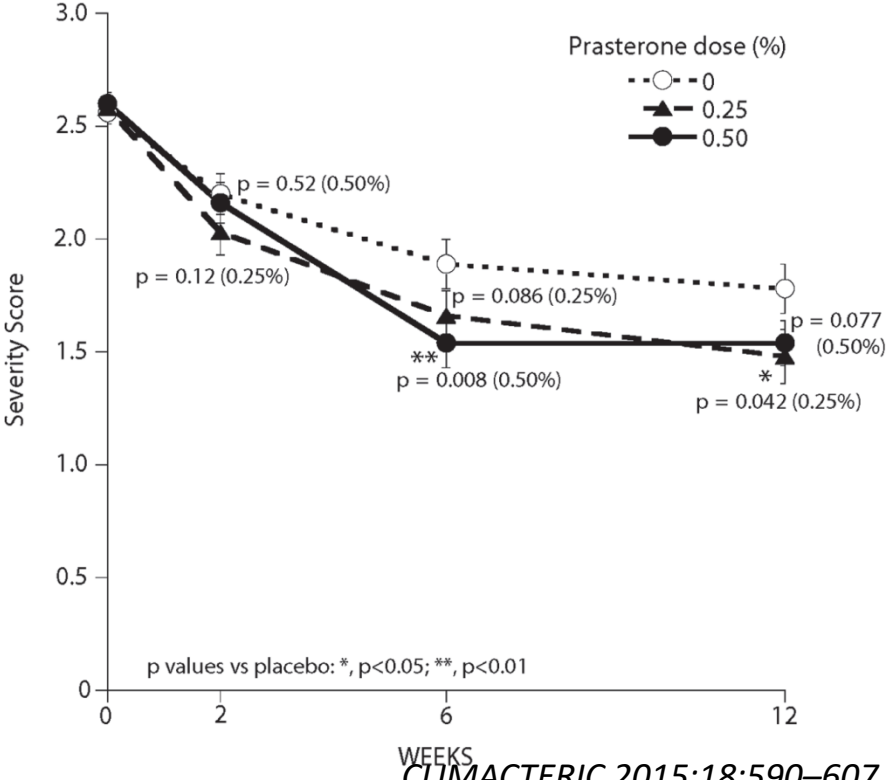
J Sex Med 2015;12:2401–2412



J Sex Med 2015;12:2401–2412

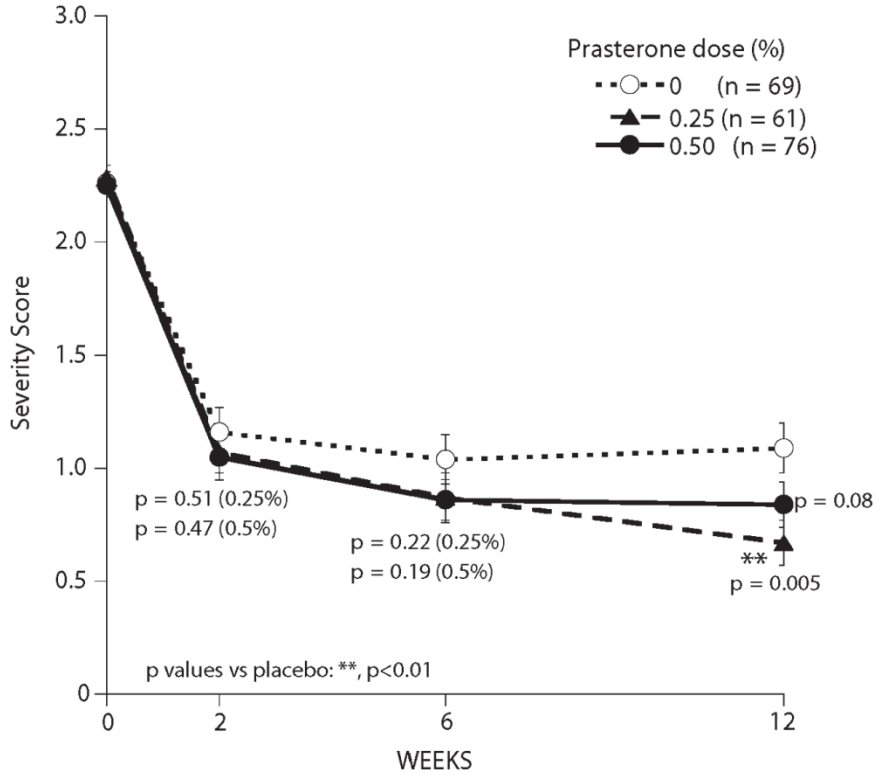
Effect of DHEA on vaginal dryness / pain at sexual activity (ITT population)





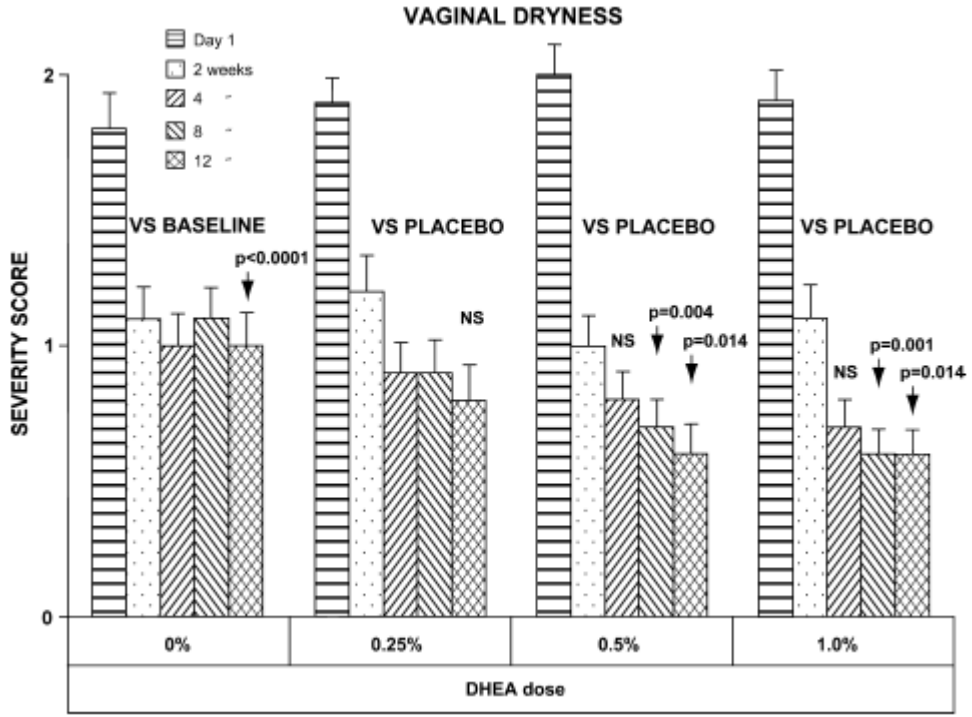
CLIMACTERIC 2015;18:590–607

Effect of DHEA on irritation/itching (ITT population)



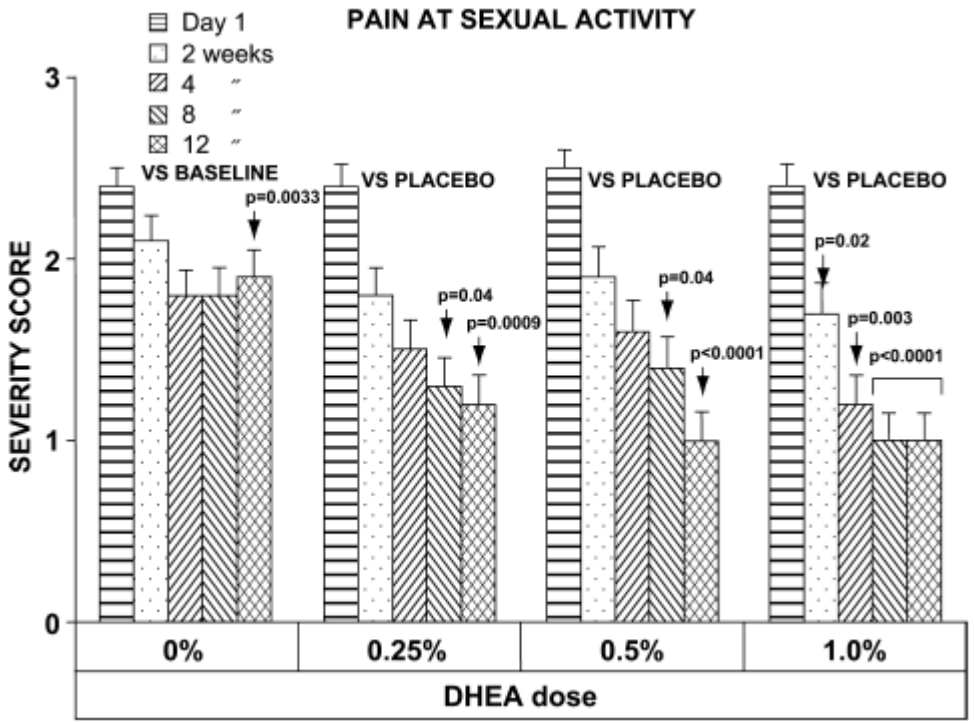
CLIMACTERIC 2015;18:590–607

Vaginal dryness



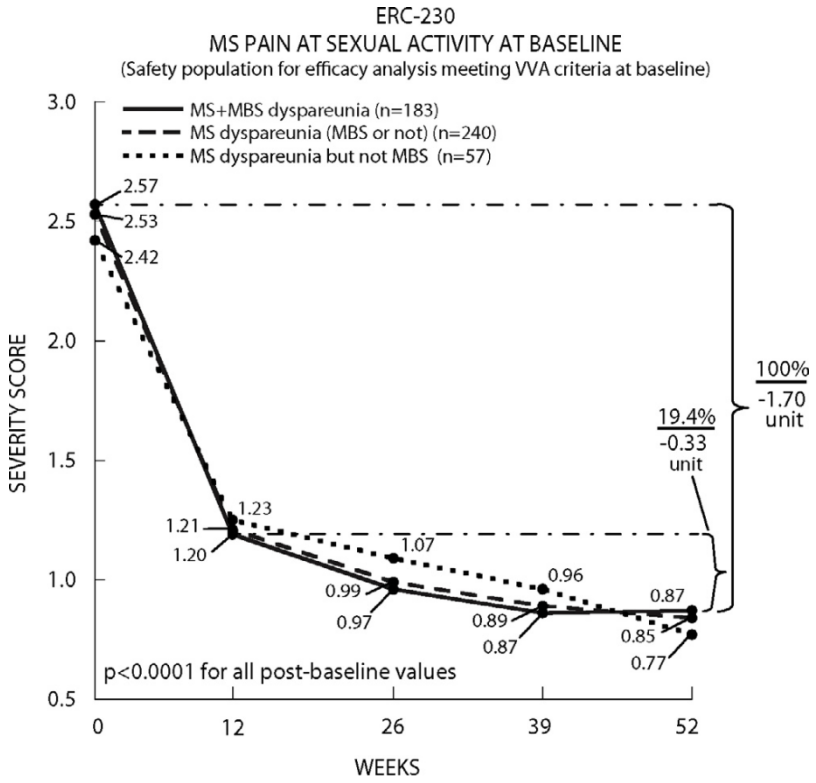
Menopause: 2009;Vol. 16, No. 5, pp. 907/922

Pain at sexual activity



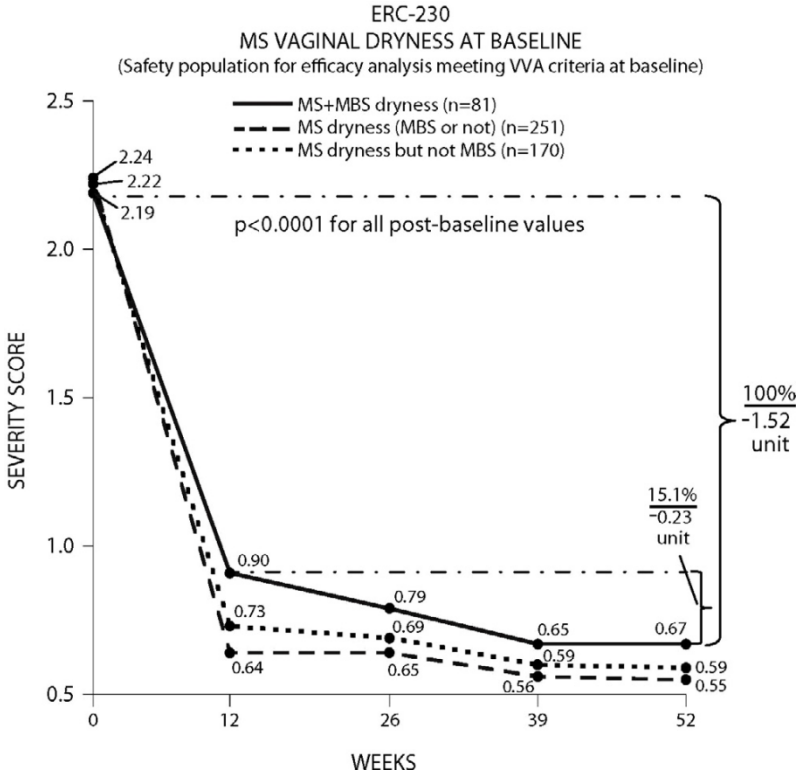
Menopause: 2009;Vol. 16, No. 5, pp. 907/922

Effect of prasterone on MS or MBS pain at sexual activity



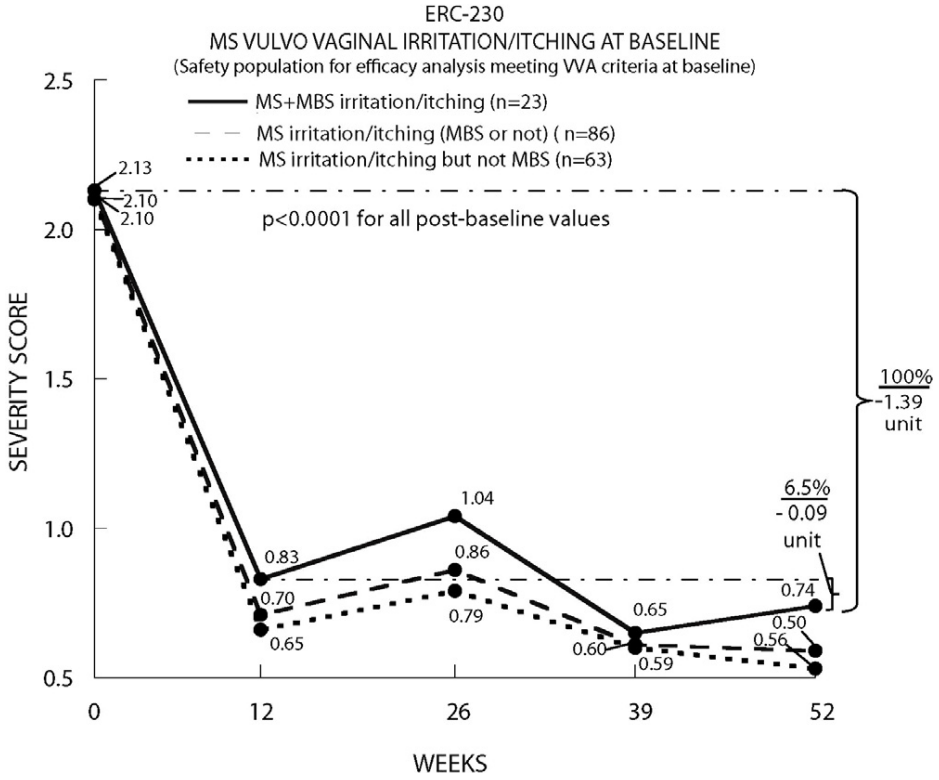
Maturitas 81 (2015) 46–56

Effect of prasterone on MS vaginal dryness

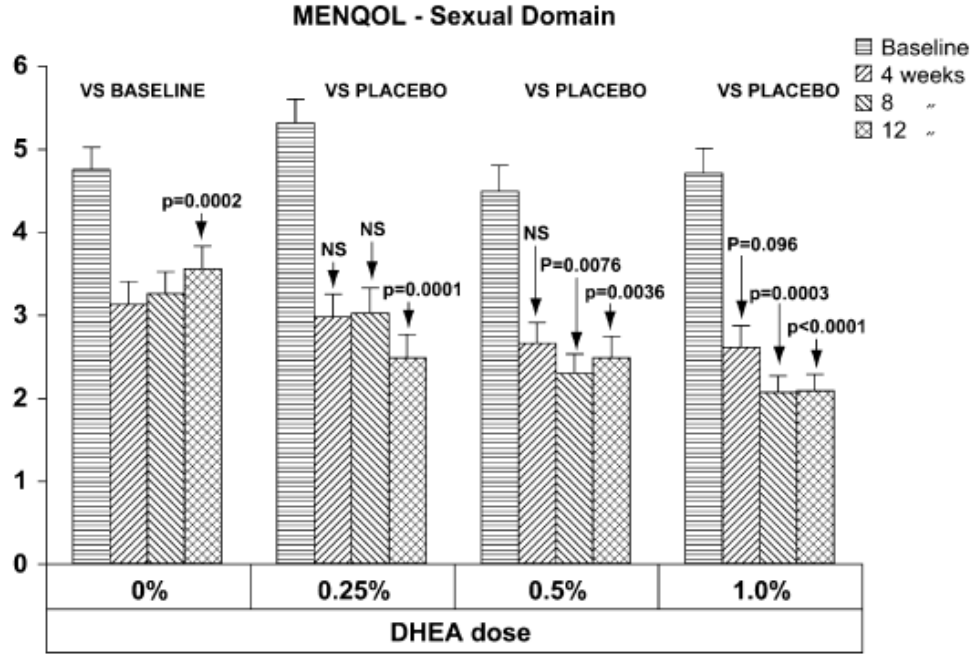


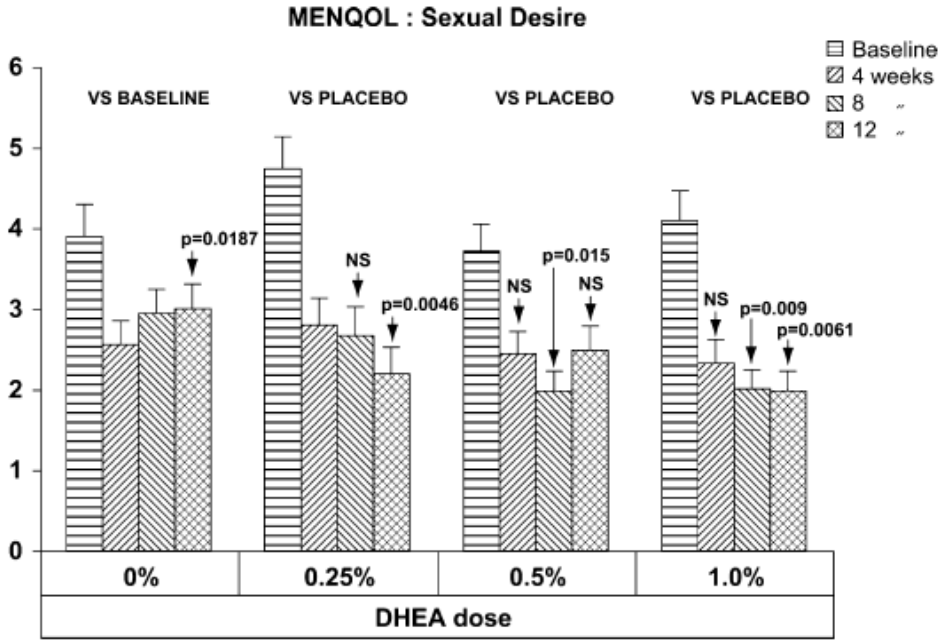
Maturitas 81 (2015) 46–56

Effect of prasterone on MS irritation/itching

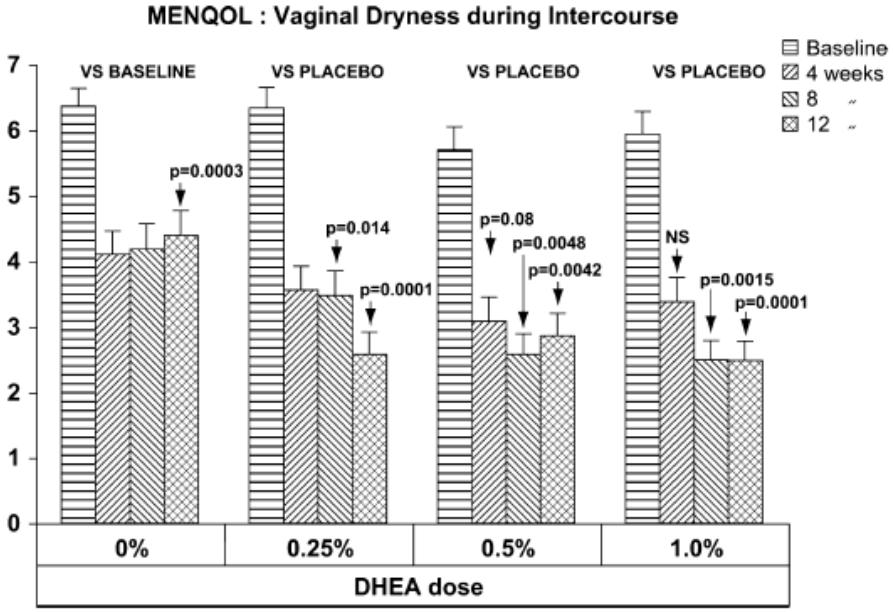


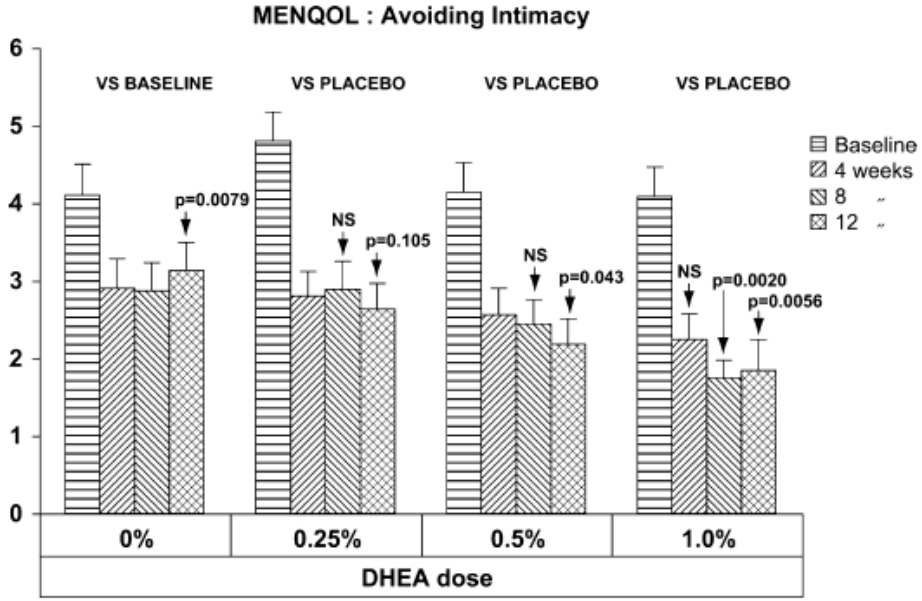
Maturitas 81 (2015) 46–56



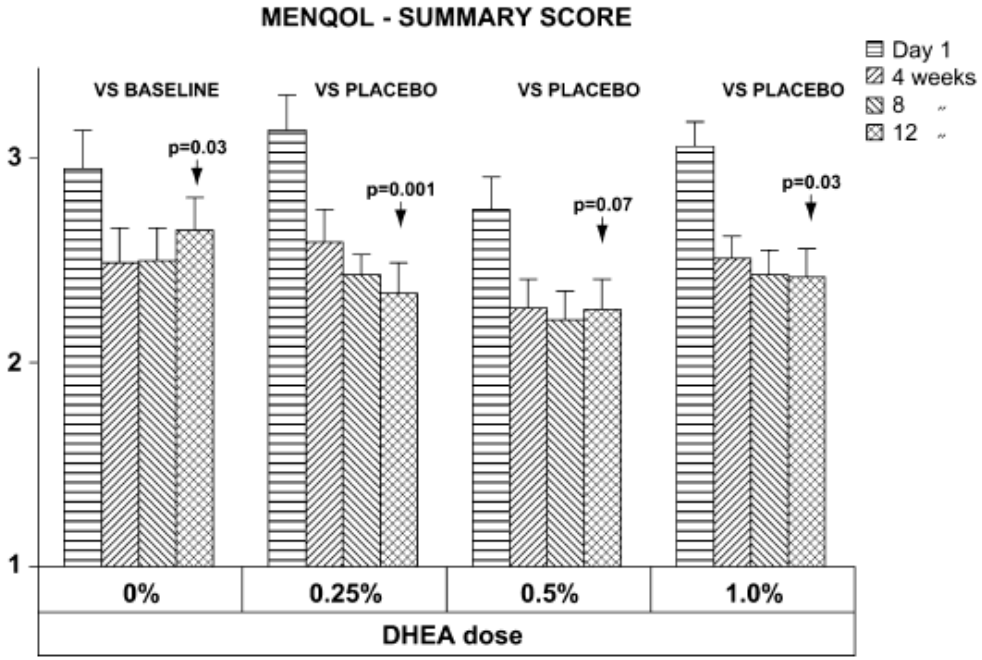


Menopause: 2009; Vol. 16, No. 5, pp. 923/931

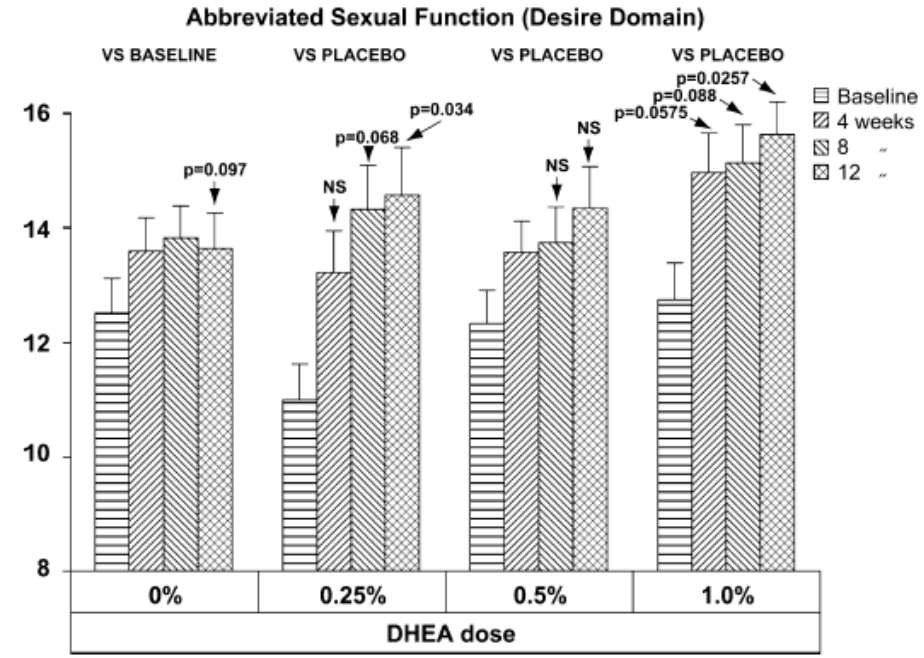


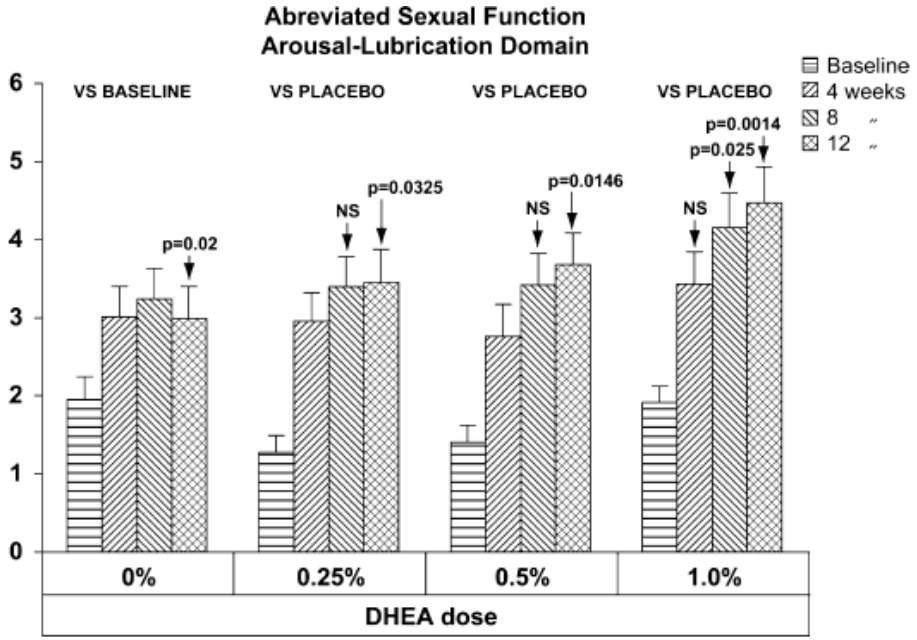


Menopause: 2009; Vol. 16, No. 5, pp. 923/931

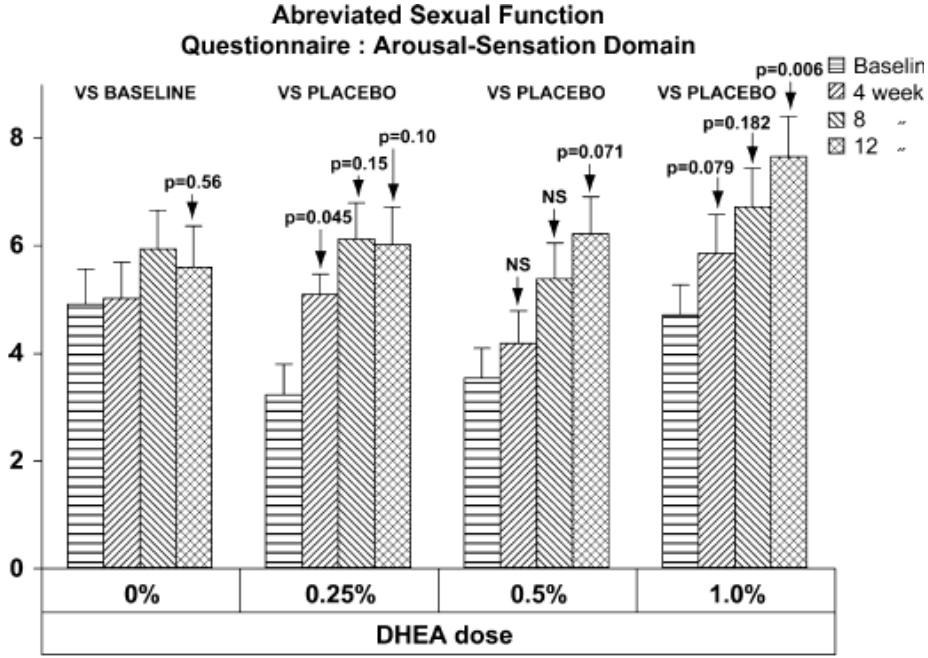


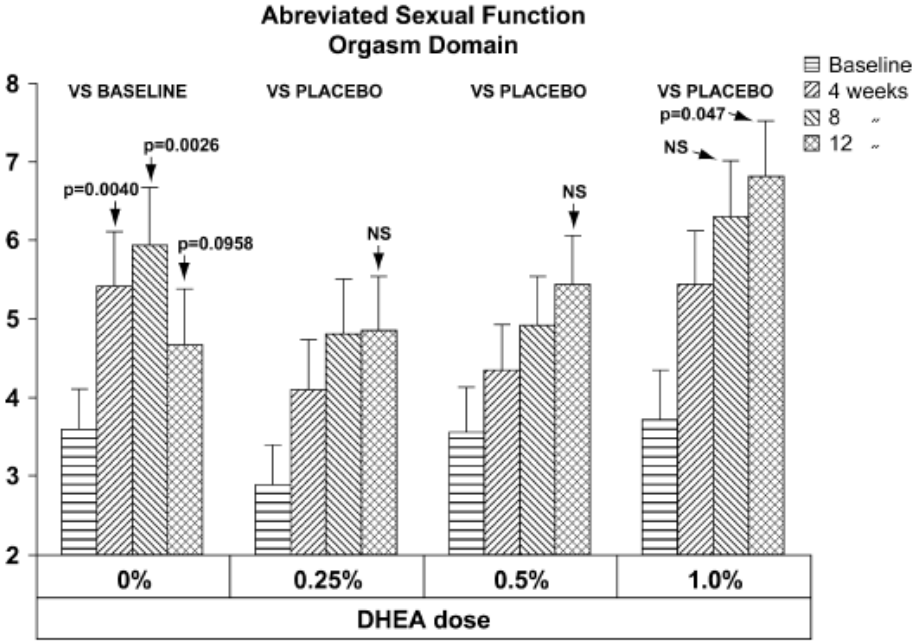
Menopause: 2009; Vol. 16, No. 5, pp. 923/931



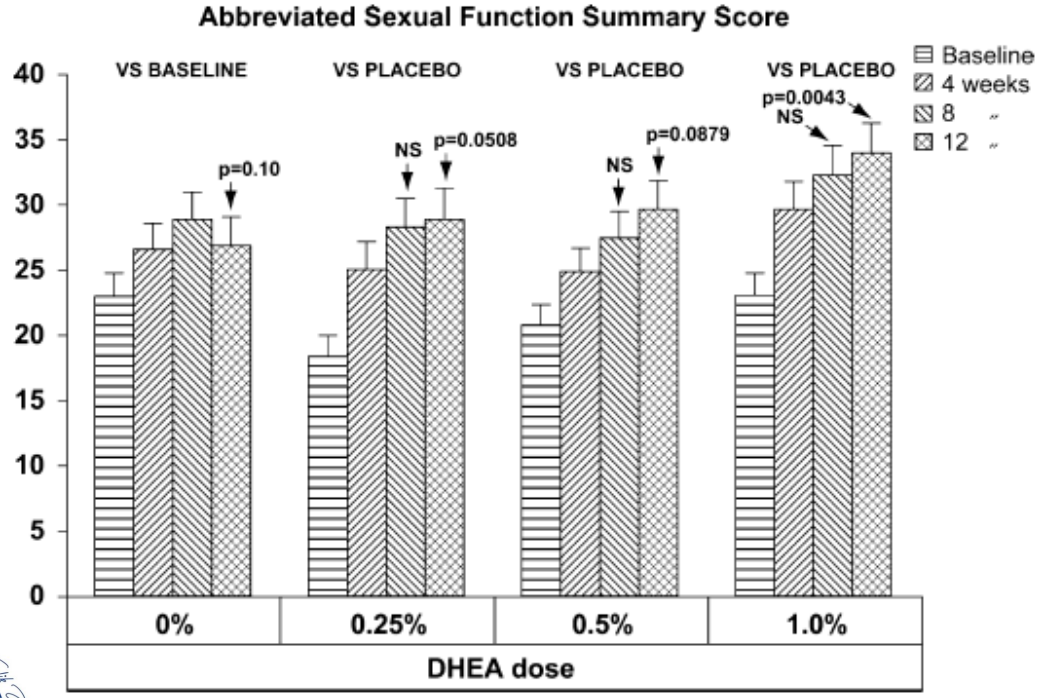


Menopause: 2009; Vol. 16, No. 5, pp. 923/931





Menopause: 2009; Vol. 16, No. 5, pp. 923/931



Menopause: 2009; Vol. 16, No. 5, pp. 923/931

phyto-SERM – summary of laboratory studies

Study	*Objective*	*Methods*	*Main results*
Somjen[12]	Estrogenic effects of DT56a	Effects of DT56a and DT56a + raloxifene on vascular animal tissues (aorta and left ventricle of heart)	DT56a has similar effects on vascular tissues like that of E2, probably mediated via common receptor(s)
Somjen[14]	Estrogenic effects of DT56a	Effects of E2, DT56a and DT56a + raloxifene on bone and cartilage of immature or ovariectomized female rats, by measuring changes in specific activity of BB isozyme of CK	DT56a acts as a SERM stimulating skeletal tissues without affecting uterus
Somjen[10]	Estrogenic effects of DT56a	Effects of long-term treatment (2 months) with DT56a on skeletal tissues of intact and ovariectomized adult rats	DT56a was as effective as E2 in reversing bone changes in Wistar OVX rats
Somjen[6]	Estrogenic effects of DT56a	Effects of DT56a *in vitro* on human-derived bone cultured osteoblasts, by measuring its effects, at different concentrations, on DNA synthesis, CK and AlP specific activities as well as changes in intracellular [Ca^{2+}] concentrations	DT56a stimulated sex-specifically female-derived osteoblasts, indicating its unique nature compared to compounds currently used for postmenopausal osteoporosis by being bone-forming and not only an antiresorptive agent
Somjen[11]	estrogenic effects of DT56a	Effects of DT56a *in vitro* on human-derived bone cultured osteoblasts when grown in HG	HG increased constitutive CK but response of CK activity and DNA synthesis to E2 treatment was reduced. DT56a was found to be active (as measured by CK activity and DNA synthesis) in both normal and high. HG decreases the hormonal responsiveness and might block important effects of estrogenic compounds, most likely contributing to their decreased skeletal-preserving properties in hyperglycemic women. In osteoblasts from postmenopausal women grown in HG, ERs mRNA expressions were unchanged. In osteoblasts from premenopausal women, HG increased ERs mRNA expressions

CLIMACTERIC 2014;17:1–8

phyto-SERM – summary of laboratory studies

Somjen[4]	Interaction between DT56a and E2	Interaction between DT56a and E2, at supraphysiological doses, in different tissues in both intact and ovariectomized female rats, as well as in human cultured vascular and bone cells	DT56a is a SERM: it stimulated different parameters similar to E2, but when given simultaneously, at supraphysiological doses, inhibited these effects of E2
Oropeza[15]	Estrogenic effects of DT56a	Food supplement (3.4 or 10.2 mg/kg) and CEE (31 or 100 μg/kg) were orally administered, daily during 14 days to ovariectomized rats. At end of treatment, the following determinations were done: dry and wet uterine weight, vaginal epithelium condition, and uterine serotonin-induced contractile response. A group treated with E2 was included as control for serotonin-induced contractile response	Food supplement did not display clear estrogenic effects on vaginal epithelium, uterine weight or myometrial sensitivity to serotonin, whereas high doses of CEE showed estrogenic action
Shabat[17]	Metabolic and immunological effects of DT56a	DT56a was orally administered to mice in three animal models: leptin deficiency, high-fat diet supplementation and immune-mediated hepatitis. Liver damage and immunological status were assessed	Oral administration of DT56a promotes a hepatoprotective effect associated with an alteration in the distribution of Tregs and NKT cells

CLIMACTERIC 2014;17:1–8

phyto-SERM – summary of laboratory studies

Study	*Objective*	*Methods*	*Main results*
Pluchino[9]	Neuroendocrine effect of DT56a	Five groups of Wistar OVX rats received one of the following treatments: oral DT56a administration at doses of 6, 12, 60, and 120 mg kg^{-1} day^{-1} or estradiol valerate at a dose of 0.05 mg kg^{-1} day^{-1} for 14 days. One group of fertile and one group of OVX rats receiving placebo were used as controls. The concentration of allopregnanolone was assessed in frontal and parietal cortex, hippocampus, hypothalamus, anterior pituitary, and serum, whereas content of β-endorphin was evaluated in frontal and parietal cortex, hippocampus, hypothalamus, neurointermediate lobe, anterior pituitary, and plasma	This study demonstrated that DT56a positively affects brain neurosteroidogenesis and the opiatergic system: DT56a exerts an estrogen-like effect on selective areas related to mood, cognition, and homeostasis control, presenting a specific pattern of interaction with brain function

CK, creatine kinase; E2, 17β-estradiol; ER, estrogen receptor; SERM, selective estrogen receptor modulator; CEE, conjugated equine estrogens; ALP, alkaline phosphatase; OVX, ovariectomized; HG, high glucose concentration; Tregs, regulatory T cells; natural killer T cells

CLIMACTERIC 2014;17:1–8

Summary of clinical studies

Study	*Objective*	*Subjects and methods*	*Results*	*Conclusions*
Labos[8]	Menopausal symptoms	Prospective study with 89 postmenopausal women with climacteric symptoms, randomly assigned to receive either DT56a ($n=27$) or oral low-dose continuous combined HT ($n=26$). Symptomatic women not wishing to receive any treatment served as controls ($n=36$). Kupperman index, serum lipids and lipoproteins, calcium, as well as BMD, endometrial thickness, and mammography were assessed at baseline and at 12 months	Patients receiving HT and DT56a showed significant and independent decrease in menopausal symptoms (mean difference in Kupperman score, DT56a group: −3.98, HT group -5.601, no treatment group + 1.76, $p<0.001$). Lumbar spine BMD *T*-score was significantly lower in women receiving no treatment, as opposed to two treatment arms which showed no significant change (No treatment, baseline: −0.60, final: −0.85, $p=0.001$; HT, baseline: −84, final −0.99, $p=0.79$; DT56a, baseline -0.51, final: −0.76, $p=0.75$). No differences in femoral bone density, ET or mammography classification detected in any of treatment arms. Likewise, serum lipids or lipoproteins did not differ between 3 groups	DT56a decreased menopausal symptoms significantly and in the same degree as HT
Nachtigall[13]	Effect of DT56a on platelet function in normal and thrombophilic women	PFA-100 was used to assess platelet reactivity at baseline and after 8 weeks of treatment with DT56a (644 mg/day) in 25 symptomatic postmenopausal women with normal clotting times and 7 symptomatic women with shortened clotting times (< 61 s)	All participants reported improved symptoms during the treatment period. No significant change in closure times was found in normally clotting participants after 3 or 8 weeks of DT56a therapy ($p>0.26$). No significant change in closure time was seen in seven thrombophilic women after 3 or 8 weeks or 1 year of treatment ($p>0.26$). The regression curve for measures over time was not significant ($p=0.26$)	DT56a did not adversely affect platelet reactivity as measured by PFA closure times in symptomatic thrombophilic postmenopausal women or normal controls

CLIMACTERIC 2014;17:1–8

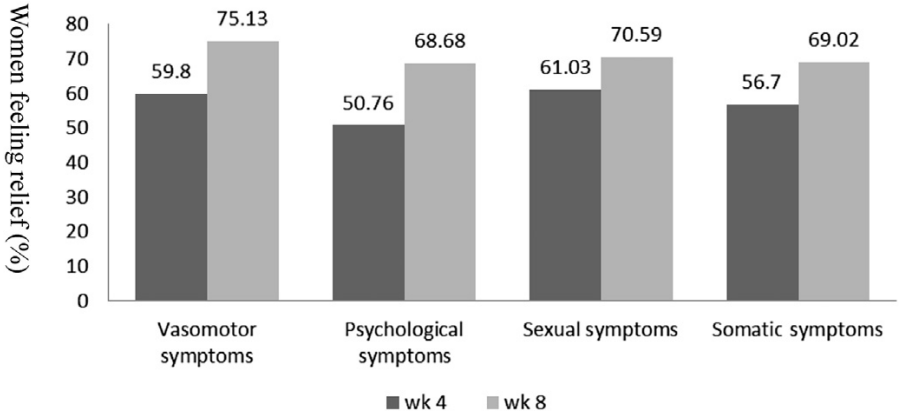
Summary of clinical studies

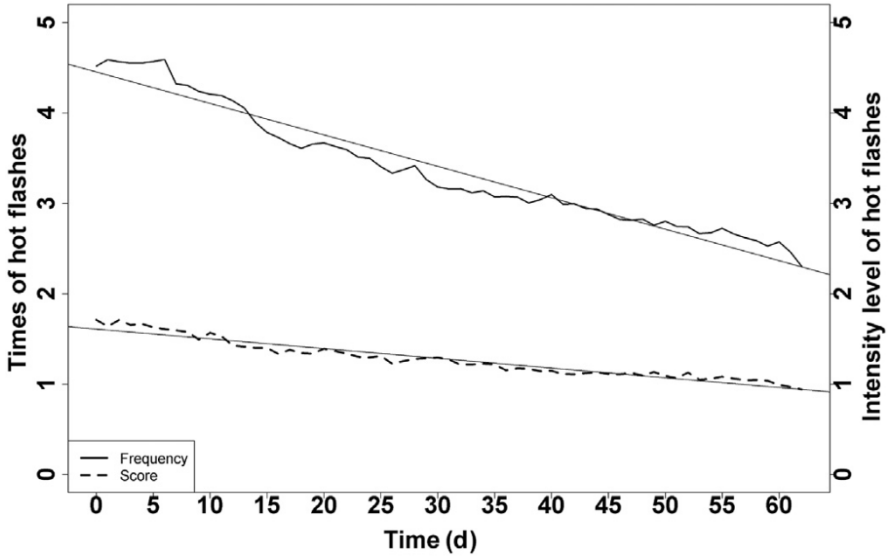
Yoles[2]	Efficacy of DT56a in preserving BMD in postmenopausal women	98 healthy, postmenopausal women randomly allocated, on double-blind basis, to receive either 644 mg/day DT56a (study group) or 344 mg/day DT56a supplemented with calcium (low-dose group) for 12 months.	BMD had increased in study group by 3.6% in lumbar spine ($p = 0.039$) and by 2.0% in the femoral neck (NS). In low-dose group, BMD had decreased in lumbar spine by 0.6% (NS) and by 0.6% in femoral neck (NS). Comparison of change in bone density between groups yielded significant difference for lumbar spine ($p = 0.037$). Neither group showed change in endometrial thickness and sex hormone levels nor reported any side-effects of treatment	DT56a increases BMD without unwanted estrogenic effect
Yoles[7]	Efficacy and safety of 2 doses of DT56a	80 postmenopausal women randomly allocated to receive either SD or LD of DT56a (644 mg/day vs. 344 mg/day). A detailed Kupperman index for each patient was completed. 12 months	In both groups there was significant reduction in Kupperman index following 12 weeks of treatment, which was sustained throughout the 12 months ($p < 0.01$). 76% of the patients in SD group reported a decrease in vasomotor symptoms and 78% in LD group (NS). This decrease was sustained following 12 months of treatment. There was no change in TSH and sex hormone levels or ET during study period	Menopausal symptoms were reduced similarly by LD and SD; however for combined treatment of menopausal symptoms and osteoporosis, the standard dosage of 644 mg/day of DT56a is needed

BMD, bone mineral density; HT, hormonal treatment; PFA, Platelet Function Analyzer; SD, standard dose; LD, low dose; ET, endometrial thickness; NS, not significant; TSH, thyroid stimulating hormone

CLIMACTERIC 2014;17:1–8

Femarelle (640 mg/d) twice daily for 8 weeks.





N=260

Taiwanese Journal of Obstetrics & Gynecology 55 (2016) 336-340

Take away messages -1

- TSEC is associated with a clinically significant reduction in the number and severity of hot flashes (GRADE 2A). This efficacy is similar to that recorded with MHT.
- TSEC is associated with clinically significant improvements in health- and sleep-related quality of life (GRADE 2B). These improvements are similar to those observed with MHT.
- TSEC decreases dyspareunia and reduces vaginal dryness compared to placebo. In addition, the use of TSEC involves significant improvements in sexual health. However, isolated VVA is not an approved indication for TSEC.

Gynecological Endocrinology, 2018; 34:10, 826-832

Take away messages -2

- TSEC is associated with a safe breast profile with the same incidence rates of breast tenderness and effect on mammary density as placebo (GRADE 2A).
- TSEC achieves high amenorrhea rates compared with placebo and significantly higher rates compared with MHT (GRADE 2A).
- TSEC exhibits a favorable endometrial safety profile with an incidence of hyperplasia similar to that of placebo (GRADE 2A).

Gynecological Endocrinology, 2018; 34:10, 826-832

Take away messages -3

Drug	Available Strengths
Oral	
Osphena (Shionogi)	60 mg ospemifene/tab
Vaginal	
Rings	
Estring (Pfizer)	2 mg/ring (0.0075 mg estradiol/d)[c]
Femring (Allergan)	0.05, 0.1 mg estradiol/d[c]
Inserts	
Intrarosa (Endoceutics)	6.5 mg prasterone/insert
Vagifem (Novo Nordisk)[d]	0.01 mg estradiol/tab
Creams	
Estrace (Allergan)	0.01% cream (0.1 mg estradiol/gram)
Premarin Vaginal Cream (Pfizer)	0.625 mg conjugated estrogens/gram

JAMA October 24/31, 2017 Volume 318, Number 16

Clinical Considerations for Women With a Uterus

Neutral Positive Potential risk

Target	E oral CE 0.625 mg	EP Oral CE/MPA	SERM RLX	TSEC 2-y data
Breast	⚪	🔴	🟢	⚪
Uterus	🔴	⚪	⚪	⚪
Vasomotor	🟢	🟢	▲	🟢
Vagina	🟢	🟢	⚪	🟢
Bone DEXA	🟢	🟢	🟢	🟢
DVT/PE	🔴	🔴	🔴	⚪ 🔴
Lipids	🟢	🟢	🟢	🟢

Summary: Clinical Use of FDA-approved SERMs/ERAAs

- For prevention of breast cancer
  - Tamoxifen and raloxifene
- For prevention of bone loss and breast cancer
  - Raloxifene
- For treatment of postmenopausal dyspareunia
  - Ospemifene
- For hot flashes and prevention of bone loss
  - TSEC CEE/BZA
- SERMs may have other benefits in their profiles that may be taken into account on an individual basis

Marmara University

https://www.slideshare.net/dryoldemir

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tyoldemir

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Summary: TSEC CE 0.45 mg and 0.625 mg/BZA 20 mg Estrogen Agonist on VMS, VVA, and Bone; Neutral on Uterus and Breast

- Significant reduction in menopausal symptoms
  - Improvements in VMS[1-3]
  - Improvement in measures of VVA[1,4,5]
- Significant increases in BMD and decreased bone turnover[6]
- Low incidences of breast pain/tenderness[1]
- High rates of amenorrhea, similar to placebo[7]
- Low incidences of endometrial hyperplasia[8]
- No changes in mammographic breast density[9]

1. Lobo RA, et al. *Fertil Steril*. 2009;92(3):1025-1035.
2. Pinkerton JV, et al. *Menopause*. 2009;16(6):1116-1124.
3. Utian W, et al. *Maturitas*. 2009;63(4):329-335.
4. Kagan R, et al. *Menopause*. 2010;17(2):281-289.
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6. Lindsay R, et al. *Fertil Steril*. 2009;92(3):1045-1052.
7. Archer DF, et al. *Fertil Steril*. 2009;92(
8. Pickar JH, et al. *Fertil Steril*. 2009;92(3
9. Harvey JA, et al. *Endocr Rev*. 2011;32(3) Abstract P1-79.

Pinkerton JV, et al. *J Clin Endocrinol Metab*. 2014;99(2):E189-E198.

NAMS
The North American Menopause Society

Who Are Not Good Candidates for TSECs (CE 0.45 mg/BZA 20 mg)?

- Elevated risk of venous thromboembolism
- Prior breast cancer (not tested in RCT)
- Prior uterine cancer (not tested in RCT)
- Symptoms not improved on CE/BZA
- Important points
  - CANNOT mix just any estrogen and SERM/ERAA—very specific effects from both
  - No data on switching from EPT to TSEC
  - Longest published trial has been 2y